Journal of Clinical Neuroscience 22 (2015) 1005–1011

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Clinical Study

Lamotrigine-induced severe cutaneous adverse reaction: Update data from 1999–2014

Xiang-qing Wang *, Bin lv, Hong-fen Wang, Xu Zhang, Sheng-yuan Yu, Xu-sheng Huang, Jia-tang Zhang, Cheng-lin Tian, Sen-yang Lang

Department of Neurology, The Chinese People's Liberation Army General Hospital, 28 Fuxing Road, Beijing 100853, China

ARTICLE INFO

Article history:
Received 3 July 2014
Accepted 4 January 2015

Keywords:
Antiepileptic drugs
Lamotrigine
Stevens–Johnson syndrome
Toxic epidermal necrolysis

ABSTRACT

We systematically reviewed and analyzed published patients with Stevens–Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) associated with lamotrigine therapy to identify characteristics of these reactions. We identified a total of 70 patients (42 SJS, five SJS/TEN, 23 TEN). The female to male ratio was 2.83:1 in the TEN group and 1.47:1 in the SJS group. Patients in the TEN group were younger than in the SJS group but this difference was not significant (28.35 *versus* 32.71 years, respectively; $p = 0.27$). The median time to onset was 25.33 *versus* 18.42 days for SJS and TEN, respectively. The median dosage at onset was 36.46 *versus* 57.29 mg, and final dosage 111.25 *versus* 97.92 mg/day for SJS and TEN, respectively. The median final dosages did not significantly differ. Concomitant use of valproate acid was reported in 54.55% of the SJS patients and 50.00% of the TEN patients. Three fatal reactions were reported, of which two patients deteriorated rapidly and died within 12 h of admission, indicating that this disease can develop rapidly before effective treatment. There was no significant difference between the SJS and TEN groups in any of the clinical factors examined which confirmed the opinion that SJS and TEN are part of a single disease spectrum.

1. Introduction

Lamotrigine, a phenyltriazine, is chemically unrelated to existing antiepileptic drugs. It is extensively metabolized, predominantly by N-glucuronidation, whereas only minor fractions undergo N-oxidation and N-methylation. It has a wide range of efficacy for partial and generalized seizures and is being investigated for a variety of additional indications such as bipolar disorders [1], cocaine abuse [2] and trigeminal neuralgia [3]. Rash of any type occurrs in 10% of patients receiving lamotrigine in controlled trials. In most patients, lamotrigine-associated rash is benign, however, serious rashes may occur such as in anticonvulsant hypersensitivity syndrome, Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).

SJS and TEN are now considered part of a single disease spectrum. The primary epidermal pathology in patients with SJS/TEN is large scale epidermal death as a result of apoptosis. SJS is usually classified as having less than 10% total body surface area involvement whereas involvement of greater than 30% is classified as TEN, and between 10–30% is classified as SJS/TEN [4]. Key clinical features of SJS/TEN include a triad of mucous membrane erosions, target lesions and epidermal necrosis with detachment.

Schlienger et al. [5] reviewed lamotrigine-induced severe cutaneous adverse reactions in 1998, and identified a total of 57 patients (43 SJS, 14 TEN). Our study is focused on the years 1999–2014, to update and systematically review and analyze reported patients with lamotrigine-associated SJS or TEN and characterize the typical aspects of these reactions in association with lamotrigine therapy.

2. Methods

A comprehensive PubMed and Scopus search covering the period from January 1999 through April 2014 of English and non-English literature (with English abstracts) was conducted to identify published reports of severe cutaneous adverse reaction (defined as SJS or TEN) associated with lamotrigine. Search terms included: "lamotrigine or lamictal" and the Medical Subject Headings terms "Stevens Johnson syndrome" and "toxic epidermal necrolysis". The reference lists of all pertinent articles were also reviewed to identify any additional reports that might have been missed in the computer search. Reports for which the necessary information for causality assessment was lacking were excluded.

* Corresponding author. Tel.: +86 01055499218.
E-mail address: bjxqwang13@163.com (X.-q. Wang).

http://dx.doi.org/10.1016/j.jocn.2015.01.016
0967-5868/

Possible duplicate reports between PubMed and Scopus cases were identified on the basis of demographics and patient descriptions.

All analyses were performed using SPSS Statistics (version 14.0; IBM Corporation, Armonk, NY, USA). For statistical analysis, we used one-way analysis of variance (ANOVA) to determine the significance of differences in clinical factors between the two groups. Continuous variables were summarized as means and standard deviations, and categorical variables as numbers and percentages. Chi-squared tests were used to compare distributions of categorical variables between groups and the paired-sample t-test and ANOVA were used to compare continuous variables. Statistical significance was set at $p < 0.05$.

3. Results

We identified 70 reports that met our inclusion criteria. A flow chart of the identification process for reported lamotrigine-related SJS/TEN articles is shown in Figure 1. We included 31 patients from case reports, 33 from pharmacogenetic studies, five from

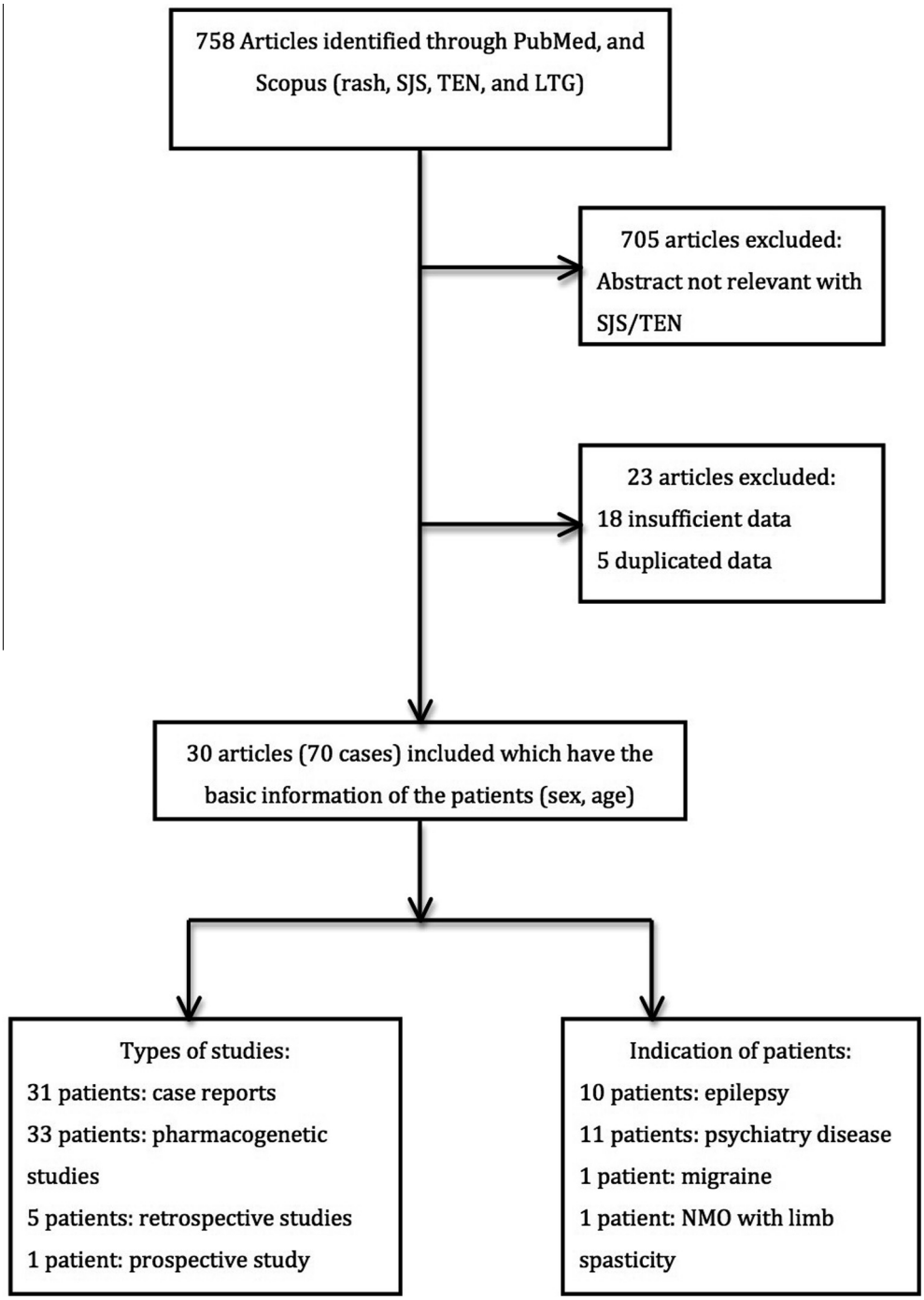

Fig. 1. Flow chart of criteria for inclusion and exclusion of lamotrigine (LTG)-related Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) reports. NMO = neuromyelitis optica.