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Original Article

Hepatitis B virus-related mortality in rheumatoid arthritis patients undergoing long-term low-dose glucocorticoid treatment: A population-based study

Sheng-Shun Yang [a,b], Chin-Tun Hung [c], Shu-Fen Li [c], Horng-Mo Lee [e], Yueh-Chin Chung [d], Hsin-Hua Chen [f], Shu-Chuan Chang [d,*]

[a] *Division of Gastroenterology and Hepatology, Department of Internal Medicine, Taichung Veterans General Hospital, Taichung, Taiwan*
[b] *Faculty of Medicine, College of Medicine, National Yang-Ming University, Taipei, Taiwan*
[c] *Department of Healthcare Administration, Central Taiwan University of Science and Technology, Taichung, Taiwan*
[d] *Department of Nursing, College of Nursing, Central Taiwan University of Science and Technology, Taichung, Taiwan*
[e] *School of Medical Laboratory Science and Biotechnology, College of Medical Science and Technology, Taipei Medical University, Taiwan*
[f] *Division of Allergy, Immunology and Rheumatology, Department of Internal Medicine, Taichung Veterans General Hospital, Taichung, Taiwan*

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KEYWORDS
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Background/Purpose: Glucocorticoids (GC) are commonly used in rheumatoid arthritis (RA) patients which bears a risk of hepatitis B virus (HBV) reactivation. The purpose of this study was to investigate the risk of HBV-related mortality under long-term low-dose GCs in Taiwanese RA patients.
Methods: We retrospectively analyzed 45,423 RA patients using National Health Insurance Research Database from January 1999 to December 2011. Of them, 2204 patients had the diagnosis of HBV and were classified into four groups according to GCs regimens. Outcome comparison by Cox model analysis for liver-related mortality was performed.
Results: In this cohort, 90.5% were older than 40. One hundred and five patients had been treated with short-term large-dose GCs (Group A); 862 patients received GCs $\geq$20 mg/day for $\geq$3 days or a variable dose but did not meet Group C criteria (Group B); 689 patients were continuously treated with low-dose ($<$20 mg/day) GCs for $\geq$3 months for at least one session (Group C); and 548 patients had never been exposed to GCs (Group D). Two hundred and sixty-one patients had been exposed

* Corresponding author.
E-mail address: sjchang@ctust.edu.tw (S.-C. Chang).

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to antiviral agents, which was significantly higher in Group C. Fifty-eight patients (2.63%) died of acute hepatic failure, while no statistically significant difference between each groups ($p = 0.074$). Groups C and D comparison by two-sample test showed that long-term low-dose GC treatment was not associated with liver-related death after adjusting for malignancy.
Conclusion: Long-term low-dose GC treatment was not associated with liver-related mortality in RA with concomitant HBV patients probably due to commonly applied antiviral therapy by rheumatologists.

Introduction

Rheumatoid arthritis (RA) is a multifactorial, chronic, autoimmune rheumatic disease (ARD) that causes progressive joint inflammation and destruction; in some patients, RA may involve different tissues or organs.[1] The prevalence is approximately 0.5%—1.5% of the general population in developed countries with an estimated incidence of 1.5 men and 3.6 women per 10,000 persons per year.[2] A nationwide longitudinal study in Taiwan recently reported that the overall incidence of major ARDs was 29.8 (95% confidence interval (CI) = 28.3—31.3) per 100,000 persons per year from 2005 to 2009 according to the national health insurance database. Among the ARDs included, the incidence of RA was the highest (17.2 per 100,000 persons per year, 95% CI 16.1—18.4).[3] In the past decade, introduction of the so-called disease modifying anti-rheumatic drugs (DMARDs), methotrexate in particular, and new biologic agents, such as tumor necrosis factor-alpha inhibitors, significantly improved RA management in some studies.[4,5] Glucocorticoid (GC), an old drug used for decades for treating RA, is effective in relieving symptoms and signs; they also demonstrate a radiological resolution through either monotherapy or combined with DMARDs.[6—8] The anti-inflammatory and immunosuppressive effects of GCs are well characterized; nevertheless, their precise mechanism of action is extremely complex and remains unclear so far; they appear to elicit different types of responses and different adverse events according to target cells, GC types, dosages, and administration routes.[9—11] The addition of low-dose (prednisone 10 mg daily or 5 mg twice daily) GC to DMARDs has been investigated in many randomized control trials, which give strong evidence of a beneficial effect of GCs on disease efficacy and on radiological resolution in early and advanced RA patients.[12]

Hepatitis B virus (HBV), a human hepatotropic DNA virus, is highly endemic in Asian countries such as Taiwan before the arrival of universal HBV vaccination; the disease has shown different stages in its natural course with a potential of being "reactivated" in some hosts who receive immunosuppressive or cancer chemotherapies.[13—16] The mechanisms by which immunosuppressive or cancer chemotherapies mediate HBV reactivation are not completely understood. The *in vitro* data suggest that steroids may regulate viral genome replication via binding to the glucocorticoid-responsive element in HBV genome.[17] Reactivation to HBV can be catastrophic and life threatening; the diverse reported rate among literature is approximately 20%—50%.[18—20] Some cancer chemotherapy agents and GCs had been associated with a higher risk of HBV reactivation in immunosuppressed patients and those with leukopenic status.[16] Most studies point out that large GC dosage is strongly correlated with HBV reactivation because of its immune suppression and the direct stimulation of HBV replication characters. Patients with low-dose or physiological dose GCs are seldom investigated. Recently, Bae et al. reported a case of a previously inactive 86-year-old HBV carrier with an acute severe flare-up during a long-term, very-low-dose glucocorticoid treatment due to RA; despite decreased viral activity after the prompt initiation of antiviral therapy against HBV, progressive liver failure and death occurred.[21] A large number of RA patients require low-dose steroid administration. Thus, re-examining the safety of low-dose steroid treatment in HBV-infected subjects is important.

The Taiwanese National Health Insurance Research Database (NHIRD) was derived from the system of Taiwan National Health Insurance (NHI) program and is maintained by the Taiwan National Health Research Institute. Each year, the National Health Research Institute collects data from the NHI program and classifies them into the NHIRD. In 2008, 22.89 million of the 22.96 million people in the country (amounting to 99.7% of the island population) were covered by the NHI program. More than 300 studies have been published in peer-reviewed journals based on the NHIRD. In the present study, we conducted a population-based cohort study to assess the outcome of HBV carriers following long-term, low-dose GC treatment in RA patients using the NHIRD.

Materials and methods

Data source

The Taiwanese NHI Program was implemented on 1 March 1995 and covers 99.7% of the country's population by year 2008. The NHIRD comprises comprehensive NHI-related administrative and claim data for research purposes. The NHI registry system for catastrophic illnesses tracks patients with major or catastrophic illnesses including RA. Patients with a catastrophic illness certificate are exempt from co-payment. At least two specialists in the Taiwan Bureau of NHI (BNHI) routinely validate diagnoses by carefully reviewing medical records, laboratory data, imaging, and pathological findings of all patients who apply for catastrophic illness

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