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ORIGINAL ARTICLE

Comprehensive analysis of hospital-based prospective cohort reveals the unique effectiveness and safety for nucleos(t)ide analogues in HBV patients

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Summary

Background: Nucleos(t)ide analogues (NAs) including lamivudine (LAM), telbivudine (LDT), adefovir dipivoxil(ADV), and entecavir (ETV) have been widely used as anti-HBV drugs. We aimed to study the effectiveness and safety of various NAs.

Methods: Two thousand three hundred and eighty patients with chronic hepatitis B (CHB) were enrolled. The rate of virologic response, optimization therapy, and serologic responses were analyzed.

Results: HBV DNA inhibitory capacity was shown to be LAM + ADV ≈ ETV > LDT > LAM > ADV. Virologic breakthrough rate and proportion of optimized treatment were LAM > ADV > LDT > LAM + ADV > ETV. However, virological response rate showed the opposite trend. The selection of anti-virals, HBeAg-negative, and lower HBV DNA levels after one year of anti-viral treatment, are favorable factors for the maintenance of virologic response.

Conclusions: This study's results were consistent with the major clinical guidelines to recommend ETV and TDF as the preferred treatment for CHB patients. LAM could be used for patients

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with lower HBV DNA load; ADV may be more applicable to non-cirrhotic patients with HBeAg-negative and lower HBV DNA load. LDT can be used to treat patients with HBeAg-positive, low HBV DNA load, and higher ALT levels due to higher HBeAg conversion rate in a baseline optimized population. The effectiveness of LAM + ADV is similar to and sometimes better than ETV treatment in a CHB population.

Introduction

Hepatitis B virus (HBV) infection can cause liver inflammation and fibrosis and may even develop into cirrhosis and liver cancer. HBV infection has become a serious social and public health problem as approximately 350 million people worldwide are infected with HBV. About 15—40% of patients with chronic HBV infection have serious complications [1,2]. More than one million people die every year from end-stage liver disease and liver cancer caused by HBV infection [3]. Hepatitis B surface antigen (HBsAg) was present in about 9.75% of the Chinese population in 1992. In nearly 20 years, HBV infection rate decreased significantly in China due to the hepatitis B vaccine, which the Ministry of Health required to be included in the ''expanded programmed immunization (EPI)'' in 2001. The National Hepatitis B Serological Epidemiological Survey in 2006 showed that the HBsAg prevalence rate has dropped to 7.18% in China. However, the 7.18% still accounted for one third of the world chronic HBV infection, including 20 million cases of chronic hepatitis B and about 300,000 cases of death from hepatitis B-related liver disease each year [4]. Therefore, the prevention and efficient treatment of hepatitis B are still causes of concern.

Anti-HBV therapy focuses on the HBV pathogen, effectively inhibits HBV replication for a prolonged period, reduces inflammatory necrosis of liver cells and fibrosis, and delays or reduces liver disease progression. Therefore, anti-HBV treatment can improve patients' quality of life and prolong survival time. Anti-HBV therapy is currently recommended as the major domestic and international SOC for chronic hepatitis B.

Anti-HBV drugs can be divided into two categories: interferon-α (IFNα) and nucleotide analogues (NAs). IFNα plays a dual role as it not only combats the virus but also modulates the immune system. The advantages of using drugs in this category are limited required treatment and a high seroconversion rate. When the long-acting interferon (Peg-IFNα) was used to treat HBeAg-negative CHB patients for one year, hepatitis B surface antigen (HBsAg) disappearance rate was 8.7% at year 3[5] and up to 12.2% at year 5,respectively [6]. However, interferon-α has a weak ability of inhibiting the virus, requires injections which have more side effects, and results in a higher proportion of patients who disrupt the treatment due to intolerance, narrow indication, and cost. Recently, the nucleoside (nucleotide) analogues (NAs) have become more widely used as anti-HBV drugs because the NAs have a stronger inhibition of HBV DNA replication. In addition, these drugs may be given orally, are easy to use, and contain less adverse reactions.

Currently, nucleoside (nucleotide) analogues, which are approved by China's State Food and Drug Administration (CFDA), are divided into three categories based on their chemical structure:

- L-nucleoside, such as lamivudine (LAM), telbivudine (LDT);
- acyclic phosphates, such as adefovir dipivoxil (ADV);
- cyclopentane/pentene, such as entecavir (ETV).

However, existing data from clinical trials with these drugs have limited number of patients with small individual differences. Therefore, the effects of these drugs on a diverse group of people need to be analyzed. The patients' condition and medication in clinical practice are different from clinical trials. When considering the various clinical factors (patient compliance, economic condition of patient, changes in disease spectrum, living and working status), the effects of the drugs, including inhibition of replication speed of HBV DNA, strength and durability, virological response rate, part virological response rate, viral breakthrough rate, the proportion of treatment adjustment, and the incidence of adverse reaction, are different from the expanded population sample. Due to the great heterogeneity of patients in clinical practice, the effectiveness, safety, and clinical outcomes of the different treatment plans still lack strong evidence-based medical support. Therefore, a real world research study based on population differentiation has been emphasized in recent years. Furthermore, since existing studies have only used single or double drug plans, multi-drugs comparisons cannot be made accurately, and clinicians can only compare results of the different studies indirectly. The differences in the different study populations may also affect the results. Thus, it is necessary to carry out a direct comparison of a variety of drugs.

A prospective study was done in a clinical setting analyzing the treatment effectiveness and safety for chronic HBV infection patients using LAM, ADV, LDT, ETV and LAM + ADV as the initial treatment. The effectiveness measure took into account biochemistry, virology, serological response, and treatment optimization or plan change rate. However, this study did not include a control group. In our present study, we compared the data from the clinical setting with various NAs treatment plans. Safety and efficiency have been analyzed with baseline optimization in a diverse, prospective cohort in order to provide stronger evidence for the benefits and costs of the various treatment plans in a clinical setting.