Persistence profile to nucleos(t)ide analogue treatment for patients with chronic hepatitis B

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ABSTRACT

Background There are currently five approved nucleos(t)ide analogues (NUCs) for the management of chronic hepatitis B (CHB): lamivudine, adefovir dipivoxil, telbivudine, entecavir, and tenofovir disoproxil fumarate.

Objective To determine the persistence rates among patients receiving NUCs for CHB at weeks 48, 96 and 144, compare them in these periods, and analyse the evolution of treatment persistence.

Methods We conducted a retrospective study that included patients with CHB who initiated antiviral therapy and were attended to by the pharmaceutical care office between January 2002 and December 2011. Patients included in a clinical trial or patients who did not collect their medication personally were excluded. There were two different analyses: a comparative analysis of the persistence rates in three periods (weeks 1–48, weeks 48–96, and weeks 96–144); and a Kaplan-Meier analysis to evaluate the evolution of persistence.

Results A total of 102 patients were included. Persistence rates were different in the three periods. They decreased during the course of the different periods, and the decline was more rapid between the first and second period. There were statistically significant differences in the non-persistence of the five drugs ($p < 0.005$). Entecavir had the best profile of persistence, followed by tenofovir.

Conclusions This study showed that high genetic barrier drugs had a better profile of persistence in the initial treatment of patients with CHB. Data seem to suggest entecavir may offer better persistence rates than tenofovir, and the persistence rates for all five medications dropped in weeks 48–96.

INTRODUCTION

Hepatitis B infection is a major global health problem with an estimated two billion people infected worldwide and 350 million chronically infected with the hepatitis B virus (HBV).¹ Approximately 600 000 patients with chronic hepatitis B (CHB) die each year due to complications of an HBV-related chronic liver disease, such as cirrhosis and hepatocellular carcinoma.²

The treatment goal of CHB is to improve long-term survival, avoiding complications such as cirrhosis, liver failure, hepatocellular carcinoma, and death.^{2,3}

There are currently five approved nucleos(t)ide analogues (NUCs) for the management of CHB. These drugs are lamivudine, adefovir dipivoxil, telbivudine, entecavir, and tenofovir disoproxil fumarate. However, these medications are rarely curative, and while they are effective in suppressing HBV replication they do not eradicate the virus.

Therefore long-term treatment is usually required to maintain viral suppression and achieve clinical benefit. Nevertheless, long duration of treatment is associated with an increasing risk of drug resistance and virological breakthrough. Medication adherence and persistence are very important to avoid the development of resistance.^{4–8}

New NUCs, such as tenofovir and entecavir, are likely to be better tolerated, have a higher genetic barrier to resistance, and are associated with lower rates of resistance than other approved CHB medications.^{9–11} In addition, these therapies offer the possibility of being used for a longer period. Health outcomes of treatment are affected by how patients take their medications and for how long. Thus, persistence should be defined and measured separately from adherence. Adherence to and persistence with medications and their impact on treatment response have been studied in some conditions. Different studies have demonstrated that inadequate adherence and non-persistence with prescribed medication regimens result in increased morbidity and mortality from a variety of illnesses, as well as increased healthcare costs.^{12–15}

Medication persistence is defined as “the duration of time from initiation to discontinuation of therapy without exceeding permissible gaps”.¹⁶ Permissible gaps must be based on the pharmacologic properties of the drug and the treatment situation. This definition was created by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Medication Compliance and Persistence Work Group; however, we can find different versions of this definition in the known studies.^{13–15}

Medication persistence is associated with appropriate drug selection, monitoring of treatment, and the individual clinical condition of the patient.^{11–18}

To date, persistence evaluation is not common, resulting in a limited number of studies on medication persistence in cardiovascular disorders, mental disorders, ulcerative colitis, diabetes, hypertension, osteoporosis and HIV.^{13–15,19} Focusing on patients with chronic hepatitis, one of these studies only determines the persistence rates over a 12 month period,⁴ whereas the other one compares the impact of persistence rates on healthcare utilisation, and cost.²⁰ Therefore, we considered that it would be interesting to analyse the persistence rates and the evolution of medication persistence concerning naïve CHB patients over a long period.

The aims of this study were to determine persistence rates among patients receiving NUCs for CHB

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at weeks 48, 96 and 144, compare them in these periods, and analyse the evolution of treatment persistence.

METHODS

We conducted a retrospective observational study that included adult patients with CHB who initiated active antiviral therapy and were attended to by the pharmaceutical care office of a pharmacy service between January 2002 and December 2011. Exclusion criteria included: patients who participated in any clinical trials or had expanded access to antiretroviral programmes; patients whose physicians did not belong to the same hospital where the drugs were dispensed; and patients who did not collect their medication personally.

The study was approved by the ethical committee of the hospital.

The main variable was persistence to NUCs. The secondary variables were: demographic (age, gender); clinical (degree of fibrosis, portal hypertension); virological (HBV genotype, hepatitis B e antigen (HBeAg), and hepatitis B surface antigen (HBsAg)); and pharmacotherapeutic (antiviral therapy, reason for switch to another NUC, and prevention of reactivation before immunosuppressive therapy or chemotherapy). Patients were stratified according to the genetic barrier of the treatment (high genetic barrier therapies: tenofovir and entecavir; and low genetic barrier therapies: lamivudine, adefovir, and lamivudine plus adefovir) and reasons for switching to another NUC (no response patients: primary no response and partial virological response; breakthrough: poor adherence, selection of drug-resistant HBV variants and others: physician decision, adverse reactions or seroconversion).

There were two different analyses: a comparative analysis of the persistence rates in three periods (weeks 1–48, weeks 48–96, and weeks 96–144); and a Kaplan-Meier analysis to evaluate the evolution of persistence. The Kaplan-Meier survival curve is defined as the probability of persistence in a given length of time while considering time in many small intervals.²¹

To determine the persistence of treatment we followed the definition developed by the ISPOR Medication Compliance and Persistence Work Group.^{16, 17} In the comparative analysis, persistence rate is a dichotomous variable measured at the end of each period. Persistence was defined as a continued acquisition of pharmacy claims for medication and no change in medication during each 12 month study period. Patients were considered to be “non-persistent” if they had a gap >15 days after the prescription or they switched to another NUC. In the Kaplan-Meier analysis, persistence is a continuous variable and was defined as the duration of time from initiation to discontinuation of treatment. In this case, patients were considered to be “non-persistent” if they switched to another drug or finished the treatment. The difference among curves was compared by using the log rank test.

Persistence rates of the first treatment were obtained through dispensing records of the pharmacy’s programme and electronic prescriptions by digital health records (Diraya). The remaining variables were obtained from microbiology reports and the medical history of each patient.

To start with, a statistical exploration of data was carried out in order to identify errors and characterise differences, followed by its respective description. Quantitative variables were summarised with means and SDs or medians and centiles with P25 and P75 in the case of skewed distributions, and qualitative variables with frequencies and percentages. This descriptive analysis was carried out for demographic data as well as treatment.

The Cochran Q test was used to compare persistence rates (expressed as percentage of patients) between study periods. We used the Kaplan-Meier method to analyse the non-persistence over the time of the study and to calculate the number of patients at risk of non-persistence each year. A value of $p < 0.05$ was considered statistically significant.

Data analysis was performed using the statistical package SPSS V20.0 for Windows (SPSS, Inc, Chicago, Illinois, USA).

RESULTS

The analysis included a total of 102 patients. Table 1 shows the general characteristics of the study population: demographic, clinical, virological, and pharmacotherapeutic.

Most of the patients were men (72.5%). The average age was 45 ± 13 years. The proportion of patients with fibrosis grade ≥ 2 was 53.00%, portal hypertension 41.3%, HbsAg positive 90.7%, and HBsAg positive 70.5%. HBV genotype D was present in about 58.3% of patients. Overall, 59.8% of patients began treatment with low barrier genetic drugs. Lamivudine was prescribed in 32.4% of patients, entecavir in 24.5%, adefovir in 17.6%, tenofovir in 15.6%, and lamivudine plus adefovir in 9.8%. The most common reason for switching to another NUC was breakthrough.

In the descriptive analysis of persistence rates, we can observe the persistence rates at different periods: weeks 1–48, weeks 48–96, and weeks 96–144 (table 2).

Persistence rates decreased during the course of the different periods, and the decline was more rapid between the first and second period. The Cochran Q test confirmed the existence of difference in persistence among these different periods ($p < 0.05$). Statistically significant differences were observed between the first period (weeks 1–48) and the second period (weeks 48–96), and between the first period and the third period (weeks 96–144) (table 3).

The Kaplan-Meier analysis by type of drug is shown in figure 1. There were statistically significant differences in non-persistence between the five drugs ($p < 0.005$). Entecavir had the best profile of persistence, followed by tenofovir. Table 4 describes the average values obtained in the Kaplan-Meier analysis for the five different medications.

The average persistence in adefovir and lamivudine plus adefovir was 46.00 (95% CI 34.07 to 57.93) and 20.20 (95% CI 9.72 to 30.68) months, respectively (log rank test: $p < 0.0005$). In the analysis of pairs of drugs, lamivudine versus lamivudine plus adefovir showed a similar profile of persistence. We found significant differences between lamivudine versus adefovir, tenofovir, and entecavir; and lamivudine plus adefovir versus adefovir, tenofovir, and entecavir (see online supplementary table S1).

In the Kaplan-Meier analysis of different types of barrier genetic drugs (figure 2), there was a statistically significant difference between low barrier genetic drugs (31.95, 95% CI 26.04 to 37.86 months) and high barrier genetic drugs (41.35, 95% CI 34.47 to 48.32 months) (log rank test: $p = 0.008$). The number of patients who switched to another NUC was larger in the lamivudine, adefovir or lamivudine plus adefovir groups than in the tenofovir or entecavir groups.

DISCUSSION

Our study showed that drugs with a better profile of persistence in the initial treatment of patients with hepatitis B were high genetic barrier drugs. Entecavir had higher persistence rates than tenofovir. In addition to this, there were differences in persistence rates in different study periods, the most important changes occurring in the second period. These data will help

Table 1 Demographic, clinics, virological and pharmacotherapeutic characteristics of the study population

Variable	N=102
Median age (SD)	45 (13)
Gender (male)	72.50%
Fibrosis ≥ 2 (n=64)	53.00%
Portal hypertension (n=63)	41.25%
HBsAg positive (n=42)	90.71%
HBeAg positive (n=78)	70.50%
Genotype (n=39)	
A	33.36%
B	5.12%
D	58.28%
E	5.12%
F	5.12%
Medication	
Low barrier genetic	59.80%
Lamivudine	32.40%
Adefovir	17.60%
Lamivudine+adefovir	9.80%
High barrier genetic	40.20%
Entecavir	24.50%
Tenofovir	15.70%
Reason for switch to another NUC (n=33)	
Non-responder	12.10%
Breakthrough	72.7%
Others	15.2%
Prevention of reactivation (n=33)	7.85%

HBsAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; NUC, nucleos(t)ide analogue.

stratify patients in order to determine the point in time to improve persistence rates.

Our study population had demographic characteristics (age and sex) similar those in the study by Chotiyaputta *et al*,⁴ although there was a difference in the treatment of hepatitis B. The principal drug prescribed was entecavir followed by tenofovir. This difference may have been on account of the fact that they included new and existing patients on NUC.

In the descriptive pharmacotherapeutic analysis, our study showed a high percentage of patients treated with lamivudine, because this drug was the current first-line therapy recommended by national and international guidelines.

Currently, there are limited studies about persistence rates in patients with CHB. In this respect, Chotiyaputta *et al*⁴ evaluates the persistence and adherence rates to NUCs in this group of patients, and also the factors associated with adherence. This study showed that persistence rates ($81.0 \pm 3.8\%$) and adherence rates ($87.8 \pm 19.1\%$) to NUCs were high, and persistence rates were higher among existing patients than among new patients.

Table 2 Persistence rates in three periods (weeks 1–48, weeks 48–96, and weeks 96–144)

Periods of time	Persistence rates N=102 (%)
Weeks 1–48	66.7
Weeks 48–96	43.1
Weeks 96–144	30.4

Table 3 Comparative persistence rates in the three periods (weeks 1–48, weeks 48–96, and weeks 96–144)

Periods of time	Difference persistence rates (%)	p Value
Weeks 1–48 to weeks 48–96	23.6	<0.005
Weeks 1–48 to weeks 96–144	36.3	<0.005
Weeks 48–96 to weeks 96–144	12.7	0.069

In our study, we found minor persistence rates. This difference could be because we only included new patients and the persistence concept was different. We defined “non-persistence” as when the patients had a gap >15 days after the prescription, while Chotiyaputta *et al*⁴ used continued acquisition medication during the study period.

The 1 year persistence rates in our study are similar to the 1 year persistence rates for statins (61.0–73.7%)^{19–22–23} and lower than for hypertensive medications (70–78%).^{24–27} Similarly, Yeaw *et al*¹² showed that patients taking an oral anti-diabetic and an angiotensin II receptor blocker had higher persistence rates than statins, prostaglandin analogues, and bisphosphonates. Patients receiving statins, NUCs, bisphosphonates and prostaglandin eye drops are asymptomatic; however, the persistence rates for hypertensive and antidiabetic medication may be high because sometimes the patients are symptomatic and they can periodically measure their blood pressure and glycaemia.

Chotiyaputta *et al*⁴ found that persistence rates decreased during the course of the year and the decline was more rapid during the first 6 months. However, our study proved that the most rapid decline was between 48 and 96 weeks (second term). This difference is mainly due to the study design (long-term). This research is useful for the stratification of patients, improving persistence, adherence and the resolution of factors that influence persistence in the pharmaceutical care consulting room.

Figure 1 Kaplan-Meier analysis by type of drug. Log rank test: $p < 0.005$.

Table 4 Mean persistence in the Kaplan-Meier analysis by type of drug

Antiviral therapy	Mean persistence, month (95% CI)
	27.84 (20.76 to 34.93)
Adefovir	46.00 (34.07 to 57.93)
Lamivudine+adefovir	20.20 (9.72 to 30.68)
Tenofovir	31.27 (25.68 to 36.85)
Entecavir	41.44 (33.01 to 49.86)

In this study, patients receiving lamivudine or adefovir (low barrier genetic) are more likely to switch to another NUC. A similar result is illustrated in our study; the worst profile of persistence was in the patients treated with lamivudine and lamivudine plus adefovir. The analysis by barrier genetic drugs showed the worst profile of persistence in low barrier agents. In this respect, Han *et al*²⁸ evaluated persistence, adherence, healthcare utilisation, and cost benefits of hepatitis B guideline recommendations. They researched into the differences in persistence, adherence and hospital stay between ‘currently recommended first-line therapy’ and ‘not currently recommended first-line therapy’.

They observed similar persistence, adherence and healthcare use between entecavir and tenofovir. Nevertheless, in the present study entecavir had a better persistence profile than tenofovir. This difference could be mainly due to the different definition of persistence used in the studies.

Currently, entecavir and tenofovir are the drugs prescribed in the treatment of CHB because these drugs have lower rates of resistance. In this study, the principal reason for switching to another NUC was a breakthrough, because there was a high percentage of patients whose first treatment was lamivudine.

Limitations

A limitation of the study relates to the retrospective design. Because of this, we used only pharmacy records to measure

persistence to treatment and all variables cannot be recollected in some patients.

Another limit to the study is that the Kaplan-Meier analysis shows average persistence rates instead of median rates due to the fact that the entecavir and tenofovir groups had few patients. The number of patients in these treatment groups was limited because these drugs only began to be used in 2008. Now they are currently recommended in first-line therapy.

Despite these limitations, this is the first report on persistence with long-term Kaplan-Meier analysis in patients with CHB. Further studies must have a large cohort, and these studies are needed to determine the factors associated with persistence to HBV medication. Adherence rates must be also analysed, because the sustained suppression of viral replication depends on prolonged saturation with the drug.

CONCLUSION

This study shows that high genetic barrier drugs had the best persistence profile in the initial treatment of patients with hepatitis B. Entecavir may offer better persistence rates than tenofovir. The persistence rates dropped in the ‘48–96 week’ period. These data will help in designing educational programmes, supporting pharmacist intervention to improve persistence with NUCs for hepatitis B, and developing a model of stratification of patients to perform pharmaceutical care.

Key messages

What is already known on this subject

- ▶ In 2008, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Medication Compliance and Persistence Work Group developed definitions for medication persistence and compliance.
- ▶ Medication persistence is defined as “the duration of time from initiation to discontinuation of therapy without exceeding permissible gaps.”
- ▶ Medication persistence is very important to promote the goal of treatment for chronic hepatitis B.
- ▶ To date, there are a limited number of studies evaluating persistence in patients with chronic hepatitis B.

What this study adds

- ▶ The best profile of persistence in the initial treatment of patients with hepatitis B were high genetic barrier drugs. Entecavir has better persistence rates than tenofovir.
- ▶ There are differences in persistence rates in different study periods; the most important change is in the second period (weeks 1–48, weeks 48–96, and weeks 96–144).
- ▶ These data will help to design educational programmes and pharmacist interventions to improve persistence of treatment with nucleos(t)ide analogues for hepatitis B and develop a model of stratification of patients to undertake pharmaceutical care.

Figure 2 Kaplan-Meier analysis by barrier genetic drug. Log rank test: $p < 0.008$.

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