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Original Article

Patients' Adherence to Tenofovir for the Treatment of Hepatitis B: The Role of Clinical Pharmacists

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Abstract

Tenofovir is an antiviral agent prescribed for patients suffering from hepatitis B. It is associated with some side effects such as reduction in the level of patients' adherence. The aim of this study was to evaluate the impact of clinical pharmacist consultation on patients' adherence to the use of Tenofovir. In this prospective study, a total of 80 patients were enrolled into the study and were divided into two groups. Patients in group one, received their medication in a routine clinic manner, while patients in the second group, by clinical pharmacist intervention, received Tenofovir along with verbal and written tips about the drug dosage, side effects, drug interactions, food-drug interactions and administration. Finally, patients' adherence to their medication was evaluated using a standard scale. Also, adverse drug reaction (ADR) occurrence and some laboratory parameters were recorded for further analysis. The patients' adherence to their medication was higher in case group than the control group in first three month of follow up. Moreover, lower ADRs were observed in patients who received clinical pharmacist consultation. It can be concluded that consultation provided by clinical pharmacist can lead to better adherence to Tenofovir usage, better therapeutic response and better tolerance of side effects.

Keywords: Adherence, Clinical Pharmacist, Consultation, Hepatitis B, Tenofovir, Viral Infection.

1. Introduction

Tenofovir is a newer anti-retroviral medication which belongs to the nucleotide reverse transcriptase inhibitor group. This agent is an effective agent for hepatitis B treatment [1, 2]. There are some important concerns regarding Tenofovir therapy. Patients who received Tenofovir may develop some adverse effects such as headache, fatigue, metabolic impairments, abdominal pain,

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nausea, alanine aminotransferase (ALT) and aspartate transaminase (AST) rises, neuromuscular problems and cough. In addition, follow up of patients should be done using some test parameters, such as serum creatinine, serum phosphorus, urine glucose, and hepatic function tests, for several months [3, 4]. Hence, the mentioned problems may dramatically affect the patient adherence to therapy. Particularly, there are some concerns that discontinuation of anti-hepatitis B medications may lead to severe exacerbations of hepatitis B infection. Therefore, it is necessary to educate the patients about their medications and follow them up to maximize their adherence to medications. Among health care providers, the clinical pharmacist practitioners play an essential role. Clinical pharmacist activities may influence the correct use of medications at three different levels: before, during and after prescription. Clinical pharmacists can enhance patients' awareness, check treatment response, and enhance the patients' adherence to their medications [5]. Therefore, they can be used to improve the patients' adherence to anti hepatitis B regimens. As a result, the patients, physicians and health systems would benefit most. The aim of the present study therefore, was to evaluate the impact of clinical pharmacist consultation on patients' adherence to Tenofovir usage.

2. Materials and Methods

This prospective study was done in the gastrointestinal and liver disease clinic of Taleghani teaching hospital. This clinic is a well-known referral center for gastrointestinal and liver diseases in Tehran and affiliated to Shahid Beheshti University of Medical Sciences, Tehran, Iran. This study was carried out between May 2016 and November 2016 and was approved by the ethics committee of Shahid Beheshti University of Medical Sciences. All patients filled the patient consent form. The inclusion criteria were as follows: patients aged 18 years and above, able to fluently speak and read Persian, newly diagnosed with chronic hepatitis B and planned to receive Tenofovir. The diagnosis of chronic hepatitis B was based on the WHO criteria. These criteria define chronic hepatitis B as the persistence of HBsAg for more than 6 months. Also, the exclusion criteria were: becoming pregnant or intent to be pregnant, HCV coinfection, HIV coinfection and patients who are candidates for liver transplantation. By considering α=0.05, β=0.8 and d= 0.65, the estimated sample size for each group was calculated. Consequently, a total of 80 patients were enrolled into study and divided randomly into two equal groups. The flowchart protocol of the study is shown in figure 1.

The patients who were in the control group received 300 mg of Tenofovir disoproxil fumarate daily without any educational

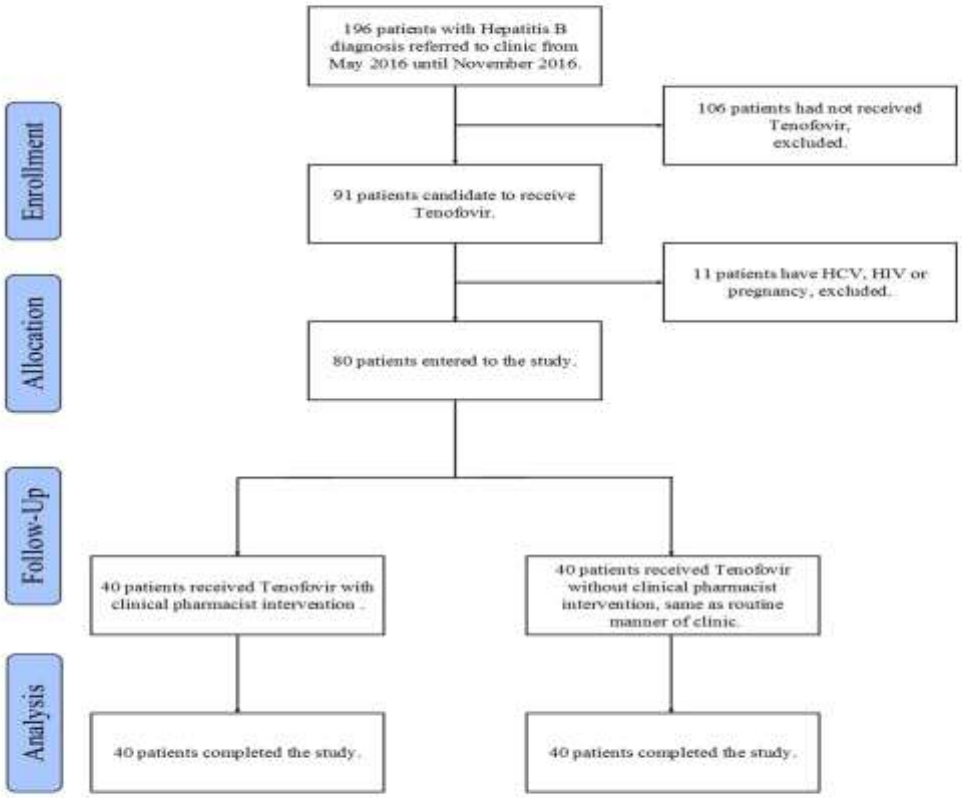

Figure 1. Flowchart protocol of current study.

intervention, while the patients in the case group received 300 mg Tenofovir disoproxil fumarate daily along with verbal and written educational package. This educational package was developed under the supervision of five clinical pharmacist experts. In this package, drug information, such as drug dosage, side effects, drug interactions, food-drug interactions and administration tips, were provided. Also, educational package was given by those clinical pharmacists working in that center, before the administration of Tenofovir. The contents of the package given to each patient were the same.

Before beginning the use of Tenofovir, the baseline characteristics of all the patients were recorded such as gender, marital status, educational level, past medical histories, family history of HBV infliction, habitual status, and residency. Patients' adherence to their medication and occurrence of any side effects were also assessed monthly for up to

six months. For this purpose, a clinical pharmacist telephoned the patients every month and their adherences to medication and occurrence of any side effects were evaluated at that point in time. The patients' adherence to their medication was quantified as presented and calculated as: the total doses of Tenofovir received by the patients divided by the total doses of Tenofovir which the patients must receive. This standard scale had been validated in a study by Steiner and *et al.* [6]. In addition, occurrence of any side effects, such as abdominal pain, nausea, diarrhea, vomiting, insomnia, headache, dizziness, and skin rash, was recorded. Occurrence of ADRs was considered as patient tolerances to their medication. However, patients with ambiguous case were referred by the pharmacist to clinic for more evaluation. Laboratory parameters, such as serum creatinine, BUN, AST and ALT, were assessed at baseline and at the end of the study.

Statistical evaluation was performed using SPSS software for Windows version 23.0 (SPSS Inc., II, USA). The descriptive statistics were presented and Kolmogorov-Smirnov test was used to determine the normality of the distribution. Consequently, the independent t test was used for parametric variables and Mann-Whitney U test for non-parametric variables. Also, Chi-square test was used to compare the qualitative variables. The significant level was considered as P value less than 0.05 and the results were reported as mean ± standard division (SD).

3. Results and Discussion

Eighty patients who met the inclusion criteria participated in this study. The demographic information of the patients are shown in table 1.

There was no significant difference between the two groups regarding age (P = 0.96), marital Status (P = 0.14), educational level (P = 0.74), past medical history (P = 0.94), family history of HBV infection (P = 0.69), habitual status (P = 0.54) and residency (P = 0.76). But the distribution of gender was significantly different between the two groups (P = 0.02).

Patients' adherence to their medication was assessed monthly for up to six months. In the first three months, significant differences between the two groups were observed (P < 0.0001, P = 0.0002 and P = 0.028, respectively), while in the second three months, no significant differences were

Table 1. Demographic information of patients participated in this study.

Patients' Adherence to Their Medication	Case Group	Control Group	*P*-value
First month	%100	%92.98±8.01	<0.0001
Second month	%100	%94.33±8.89	0.0002
Third month	%99.90±0.63	%95.80±11.31	0.028
Forth month	%100	%98.13±10.60	0.270
Fifth month	%100	%99.80±0.88	0.160
Sixth month	%100	%100	>0.999

Table 2. Patients' adherence to their medication in six month follow up period.

Variable	Groups	Base Line	*P*-value	End of Study	*P*-value
Serum Creatinine	Case Group	1.03±0.18	0.91	1.01±0.16	0.40
	Control Group	1.01±0.24		1.06±0.17	
BUN	Case Group	16.77±1.82	0.94	17.36±1.84	0.81
	Control Group	16.82±2.15		17.5±1.94	
AST	Case Group	64.18±12.35	0.98	46.21±13.03	0.03
	Control Group	65.78±11.34		57.82±10.78	
ALT	Case Group	77.02±11.32	0.98	56.18±11.14	0.04
	Control Group	75.78±10.68		66.27±32.28	

AST: Aspartate Aminotransferase; ALT: Alanine transaminase; BUN: Blood Urea Nitrogen

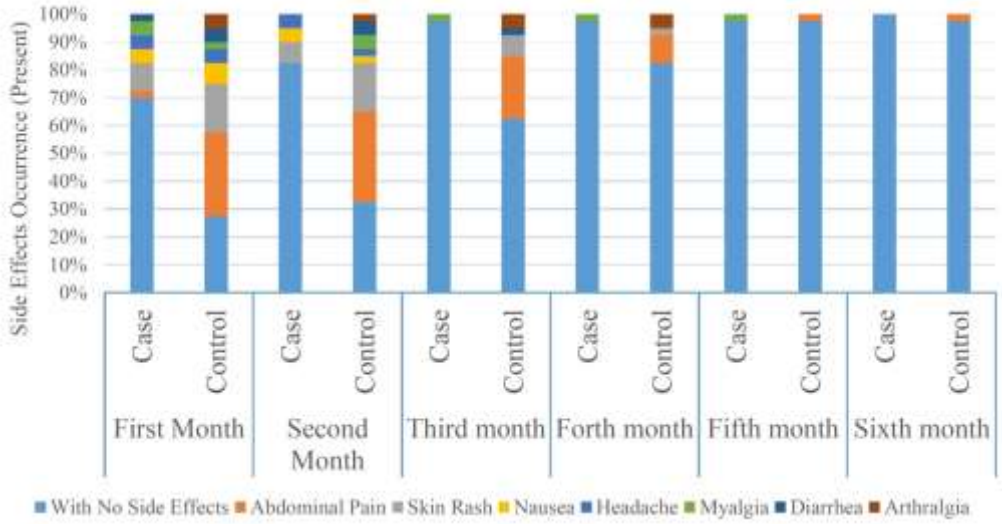

Figure 2. The occurrence rate of side effects between two groups in six months of study.

observed between the two studied groups (P = 0.27, P = 0.16 and P > 0.999, respectively). The calculated values for patients' adherence to their medication are shown in table 2.

The results of ADRs occurrence were reported monthly. These results showed significant difference between the two groups in the first three months (P=0.005, P=0.0001 and P=0.002, respectively). But the occurrence of side effects were not significantly different in the second three months (P = 0.105, P = 0.368 and P = 0.314 respectively). Main side effects which were occurred in this study as order were abdominal pain, skin rash, nausea, headache, myalgia, diarrhea, and arthralgia.

The occurrence rate of each side effects is shown in figure 2.

The results of laboratory date showed that before starting the therapeutic regimen, no significant differences were observed between the two groups. But at the end of the study, AST and ALT were significantly different between the two groups. Nevertheless, serum creatinine and BUN were not different significantly. The results of the laboratory evaluations are shown in table 3.

Patients' adherence under treatment with Tenofovir was evaluated in the present study through clinical pharmacist consultation. To the best of our knowledge, this study is the first to evaluate the clinical pharmacists' role in the optimization of adherence to Tenofovir consumption by hepatitis B patients. Patients suffering from chronic HBV were enrolled into the study and treatment with Tenofovir was initiated. A group of patients received Tenofovir under the supervision of clinical pharmacist but another group received Tenofovir without clinical pharmacist intervention. To evaluate the effect of interventions, patients' adherences to their medication was assessed as primary outcome. Also, the occurrence of side effects and some laboratory values were determined as secondary outcomes. The results indicated that there was no significant difference between the two groups in terms of demographic information. Hence, the patients were allocated to two groups unvaryingly and as a

Table 3. The results of laboratory date in base line and end point of study.

Variable		**Case Group**	**Control Group**	***P*-value**
Age (Mean±SD)		43.55±16.59	43.38±15.25	0.96
Gender [Present(Frequency)]	Male / Female	29 (%72.5) / 11 (%27.5)	19 (%47.5) / 21 (%52.5)	0.02
Marital Status [Present(Frequency)]	Single / Married	6 (%15) / 34 (%85)	2 (%5) / 38 (%95)	0.14
Educational Level [Present(Frequency)]	Under diploma and diploma / Bachelor and higher	34 (%85) / 6 (%15)	36 (%90) / 4 (%10)	0.74
Past Medical Histories [Present(Frequency)]	No history / Diabetes / Hypertension	30 (%75) / 4 (%10) / 6 (%15)	29 (%72.5) / 5 (%12.5) / 6 (%15)	0.94
Family History of HBV infliction [Present(Frequency)]	Yes / No	12 (%30) / 28 (%70)	14 (%35) / 26 (%65)	0.69
Habitual Status [Present(Frequency)]	No / Alcohol / Opium addiction / Smoking	30 (%75) / 4 (%10) / 2 (%5) / 4 (%10)	29 (%72.5) / 3 (%7.5) / 1 (%2.5) / 7 (%17.5)	0.54
Residency [Present(Frequency)]	Tehran province / Out of Tehran	28 (%70) 12 (%30)	30 (%75) 10 (%25)	0.76

HBV: Hepatitis B Virus; SD: Standard Division

result, the effects of confounding variable have reached the minimum effect. But it was observed that gender was not equivalently distributed between the two studied groups because hepatitis B is more prevalent among Iranian males [7]. The patients' adherences to their medication also were higher in case group rather than the control group. The results showed that in the case group, the patients' adherence to their medication was about 100%. While in the control group, the first three months of patients' adherences to their medication was not as perfect as the case group and in next three months, a significant improvement was observed in patients' adherences to their medication. Hence, there were no significant differences between the two groups in the second three months. This improvement is due to adaptation phenomena which allow the patients to tolerate their medication and as such, over time, the patients' adherences to their medication can be improved. This pattern was observed in case group faster than the control group due to clinical pharmacist intervention. Hence, by clinical pharmacist consultation, the patients tolerated their medications well and a better therapeutic response was achieved. The main side effects of Tenofovir are nausea, abdominal pain, diarrhea, vomiting, depression, headache, dizziness, arthralgia, myalgia, trouble sleeping, itching, rash, and changes in the shape or location of body fat [8]. As mentioned, abdominal pain, skin rash, nausea, headache, myalgia, diarrhea, and arthralgia were the main side effects which were seen in current study. The patter of occurred side effects was similar to side effects which occurred in previous studies. However, there are some reports which noticed bone related disease as a side effect of Tenofovir. These studies demonstrated the relations between cumulative exposures to Tenofovir and osteoporosis. This side effect is occurred in prolong usage, hence current study cannot detect it [9, 10]. Nasopharyngitis is another side effect of this agent which was not seen in current study. This phenomena is may be due to pharmacogenomics patter of Tenofovir side effects [11]. Nephrotoxicity of this agent has a very low prevalence and current study, similar to previous studies, did not reported it [8].

Another outcome that was assessed in this study was ADRs as a scale for measuring patient tolerances to their medication. ADRs were reported to be higher in the first months, particularly in the control group as compared with the case group. But generally, due to the tolerability phenomena, it decreased in second three months. It can be concluded that clinical pharmacist intervention may be effective in ADR tolerance by patients. Another outcome of this study was the laboratory results. Although, the base line values of the laboratory parameters were not significantly different between the two groups, the ALT and AST values were significantly decreased in the case group as compared with the control group. But this reduction was not observed in serum creatinine and BUN. These findings suggest that clinical pharmacist intervention may lead to better adherence to medication regimen and as a result, patients in the case

group received their medication more regular than the control group. It was observed that renal toxicities of Tenofovir appeared in long term usage unlike liver complications. Hence, the renal function of the two studied group was normal until the end of the study. Previous studies have evaluated the pharmacists' role in hepatitis treatment.

Langness *et al*. (2017) studied the role of clinical pharmacist in optimizing hepatitis C virus treatment. In their retrospective study, the drug-drug-interactions in patients with hepatitis C virus and the interventions made by clinical pharmacists were evaluated. They concluded that drug-drug interactions are common with hepatitis C virus medications and an interdisciplinary team including a clinical pharmacist can optimize patient care [12]. Martin *et al*. (2016) studied the patient satisfaction regarding clinical pharmacist consultation and prescribers during hepatitis C virus management. The patients in their study reported high satisfaction levels with the clinical pharmacist involved in hepatitis C treatment [13]. Moreover, Rodis *et al.* (2010) studied the medication adherence and quality of life in patients with hepatitis C virus receiving combination therapy. In their study, the patients received a structured education about HCV medications and were monitored monthly through phone call from a pharmacist regarding their therapy. Similar to the present study, they used telephone to follow up their patients. In this method, patients express their own medical condition and it is suitable for patients who are living far away from clinic. After 3 months, they evaluated the adherence, satisfaction, and quality of life. The findings of their study showed that patients who received medications under the supervision of pharmacists had high adherence rates and were satisfied with the provided care. Also, they found that the quality of life may be associated with adherence [14]. In another study, Marino *et al*. (2009) evaluated the pharmacist interventions in optimizing therapeutic response in patients with chronic hepatitis C virus infection. They found that pharmacists are in a good position to increase the treatment response as part of the multidisciplinary patient care team [15]. Recent studies had demonstrated that pharmacist interventions and pharmacotherapy consults can significantly reduce ADR occurrence. These studies are performed in hospitals and ambulatory clinics [16-18]. Krska *et al*. (2001) also found that ADR occurrence relative risk reduces after pharmacist interventions [19]. The reduction in ADR occurrence by patients can decrease patient morbidity and mortality. Also, significant cost savings by preventing hospitalizations and medication costs are expected [20-22]. The results of current study in point of ADR reduction confirm the results of previous studies.

The main limitation of current study was the short period of study. In addition it is suggested to evaluate the adherence through other direct or indirect methods.

4. Conclusion

In conclusion, the results of the present study showed a positive impact of clinical pharmacist in hepatitis B treatment. The

provided consultation by clinical pharmacist can lead to better adherence to medication regimen, better therapeutic response and better tolerance of side effects.

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