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Quality of Life of Chronic Hepatitis B Patients Consuming Nucleoside Analog: A Case-Control Clinical Study in Indonesia

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ABSTRACT

Introduction: Chronic hepatitis B raises serious concern due to its high morbidity, such as cirrhosis and hepatocellular carcinoma, and mortality from 267 per 100,000 person-years. Up to now, medical therapy that successfully eradicates the hepatitis B virus is not available. Therapy is given in the long term for suppressing viral replication and disease progression. Nucleoside analog (NA) is a medication that is consumed orally once a day for years. Previous studies showed that patients who were treated with NA had a different quality of life (QoL) compared to naïve patients. This research aimed to analyze the QoL of chronic hepatitis B patients who consumed NA by comparing it with naïve patients at Dr. Soetomo General Academic Hospital Surabaya.
Methods: Subjects were recruited consecutively from chronic hepatitis B patients at Dr. Soetomo General Academic Hospital Surabaya during 9 February – 31 May 2021. Data about sociodemographic characteristics, hepatitis B therapy history, and QoL were gained by using the SF-36 questionnaire and medical records. Subjects were divided into NA and naïve groups which responses underwent an analytical comparison.
Results: NA group had significantly higher QoL in physical component score (PCS) and mental component score (MCS), with physical functioning (PF), role limitations due to physical health (RP), role limitations due to emotional problems (RM), energy/fatigue (VT), emotional well-being (MH), social functioning (SF), and general health perception (GH) subscales having $p<0.05$
Conclusion: The QoL of patients who were treated with NA was significantly higher than that of naïve patients in terms of physical and mental components.

Introduction

Chronic hepatitis B (CHB) infection remains a health problem that takes the attention for its global eradication due to high incidence and complications. Globally, it is estimated that every 1 per 3 people suffers from CHB with seven hundred and eighty thousand deaths per year.[1] Indonesia was the country with second highest hepatitis B cases after Myanmar in Southeast Asia.[2] The prevalence in Indonesia was declined from 9.4% in 2007 to 7.1% in 2013, implying that the country had moderate case of the disease recently.[3] North Sulawesi (33%) and Papua (12.8%) had the highest HBsAg prevalence and Pontianak had the highest hepatitis B viral (HBV) infection (9.1%) compared to other areas in Indonesia.[4] Considerable incidences were caused by behavior associated with transfer of HBV via body fluids. Among several risk factors related to the probability of hepatitis B infection to become chronic,

horizontal transmission from mother-to-child during pregnancy and birth was marked due to higher CHB probability to child. Studies indicated 4.7% pregnant women in West Java, 3.4% in Mataram, and 2.2% in Jakarta had positive HBsAg.[3] This phenomenon needs to get the concern related to the health burden due to its CHB status in the future.

CHB therapy is given by considering clinical and non-clinical criteria, including HBsAg, HBeAg, serum ALT level, HBV DNA, liver fibrosis stadium, cost, duration of therapy, and individual condition.[5–7] Nucleoside analog (NA) is an antiviral agent that competes with nucleoside or nucleotide to prematurely terminate viral relaxed circular DNA (rcDNA) during reverse transcription that inhibits HBV replication.[8] There are 5 NA available regimens: lamivudine, adefovir, entecavir, telbivudine, and tenofovir. NA is consumed orally for each day until HBsAg is undetectable, HBeAg seroconversion without cirrhosis, or HBV DNA is undetectable for a minimum of 12 months after a complete treatment.[9] Complex pathophysiology causes the need to consume NA for years in Indonesia, frequently without a fixed duration of therapy.

QoL is an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns.[10] Health status and drug use influence QoL through physical and mental health.[11] According to the long-term use, CHB patients who receive NA therapy have potency of suffering from QoL change.

Patient' QoL affects disease prognosis. Therefore, QoL needs to be involved in therapy. To the best of our knowledge, there was no research conducted on QoL in CHB patients consuming NA in Indonesia. Therefore, this study aimed to analyze QoL comparison in CHB patients receiving NA and naïve patients.

Methods

Sample

This is a cross-sectional study in CHB patients diagnosed at the Unit of Hepatology, Department of Internal Medicine, Dr. Soetomo General Academic Hospital Surabaya during 9 February – 31 May 2021. Inclusion criteria were patients aged at least 20 years old, had been consuming NA for at least 12 months or were still naïve, ambulatory, understood Bahasa Indonesia, and competent to respond. Exclusion criteria were pregnant women, had other chronic diseases, and history of interferon therapy. Patients were divided into NA group and naïve group with of 93 and 66 patients for each group.

Data Collection

Patients' QoL were measured using the Indonesian version of The Short Form 36 Health Survey (SF-36) that had passed validity and reliability requirements.12 SF-36 consists of 36 items to measure physical component score (PCS) and mental component score (MCS). PCS subscales include physical functioning (PF), role limitation due to physical health (RP), pain (BP), and general health perception (GH). MCS subscales include role limitation due to emotional health (RM), energy/fatigue (VT), emotional well-being (MH), and social functioning (SF). A higher mean score indicates better QoL assessed by related variables. Patients' sociodemographic and NA regimen data were taken together with SF-36 completion. Medical records were used to ensure and complete the data.

Statistical Analysis

Data were statistically analyzed by using IBM SPSS 26th version. Descriptive analysis included gender, age group, highest educational attainment, and NA regimen. Distribution normality was assessed by using Kolmogorov-Smirnov Test. Analysis of QoL comparison between groups was assessed by using Independent Mann-Whitney U Test with $p < 0.05$.

Ethical Approval

This study had received ethical approval from Medical Research Ethics Committee of Dr. Soetomo General Academic Hospital Surabaya with number 0144/KEPK/II/2021. Informed consent for participation was attached at the beginning of the questionnaire.

Results

CHB patients were dominantly male in both group (67.70% vs 65.20%). Most patients were 41 – 50 years old at the time answering the questionnaire (30.10% vs 34.80%). The youngest and oldest patients were 20 and 65 years old in NA group and 21 and 69 years old in naïve group. Senior high school was the highest education attained by most of the patients in both groups (52.70% vs 51.50%). All sociodemographic characteristics are presented in Table 2.

Most patients in NA group were consuming tenofovir (84.90%). Other regimens prescribed were telbivudine (7.50%), lamivudine (5.40%), and entecavir (2.20%), with no patients treated with adefovir at the time answering the questionnaire. Data are presented in Table 1.

Table 1. Nucleoside Analog Regimen Consumed by Patients

Regimen	NA Group (n, %)
Tenofovir	79 (84.9)
Telbivudine	7 (7.5)
Lamivudine	5 (5.4)
Entecavir	2 (2.2)
Adefovir	0 (0)

Annotation: NA, Nucleoside analog

NA group had significantly higher mean score in PCS (84.71 vs 76.16, p=0.004) and MCS (83.02 vs 75.63, p<0.001). Only three PCS subscales were significantly higher in NA group: PF (88.17 vs 82.57, p=0.043), RP (85.4839 vs 75.3788, p=0.027), and GH (72.4194 vs 62.95, p<0.001). BP was insignificantly higher in NA group than naïve group (92.68 vs 83.75, p=0.059). All MCS subscales were significantly higher in NA group: RM (95.70 vs 90.40, p=0.047), VT (71.02 vs 62.65, p<0.001), MH (73.54 vs 65.21, p<0.001), and SF (91.80 vs 84.28, p<0.001). All SF-36 components are attached in Table 3.

Table 2. Sociodemographic Data of Patients

Variable	NA Group (n, %)	Naïve Group (n, %)
Gender		
Male	63 (67.70)	43 (65.20)
Female	30 (32.30)	23 (34.80)
Age group (year)		
<21	0 (0)	1 (1.50)
21 – 30	15 (16.10)	12 (18.20)
31 – 40	18 (19.40)	15 (22.70)
41 – 50	28 (30.10)	23 (34.80)
51 – 60	26 (28.00)	10 (15.20)
>60	6 (6.50)	5 (7.60)
Mean + SD	44.53 + 11.42	42.38 + 11.82
Educational Attainment		
No school	2 (2.20)	1 (1.50)
Primary school	9 (9.70)	6 (9.10)
Junior secondary school	3 (3.20)	5 (7.60)
Senior secondary school	49 (52.70)	34 (51.50)
Associate degree	4 (4.30)	4 (6.10)
Bachelor's degree or higher	24 (25.80)	15 (22.70)
Others	2 (2.20)	1 (1.50)

Annotation: NA, Nucleoside analog

Table 3. QoL Comparison between Groups

Variable	NA Group	Naïve Group	p
	Mean + SD	Mean + SD	
PCS	84.72 + 15.36	76.16 + 20.52	0.004*
PF	88.17 + 16.90	82.57 + 17.72	0.043*
RP	85.48 + 28.62	75.37 + 33.53	0.027*
BP	92.68 + 14.96	83.75 + 24.48	0.059
GH	72.41 + 14.49	62.95 + 18.64	<0.001*
MCS	83.01 + 8.89	75.63 + 11.83	<0.001*
RM	95.69 + 14.92	90.40 + 22.46	0.047*
VT	71.02 + 12.34	62.65 + 10.96	<0.001*
MH	73.54 + 11.14	65.21 + 10.04	<0.001*
SF	91.80 + 13.48	84.28 + 15.85	<0.001*

Annotation: NA, Nucleoside analog; PCS, Physical component score; PF, Physical function; RP, Role limitation due to physical health; BP, Bodily pain; GH, General health perception; MCS, Mental component score; RM, Role limitation due to emotional problems; VT, Vitality; MH, Emotional well-being; SF, Social function.
*p<0.05 indicates significant difference

Discussion

CHB incidence is different in several sociodemographic variables. Previous studies supported that male patients were dominant.[13,14] Gender differences in CHB incidence are influenced by immune characteristics, estrogen protective effect, and exposure to high-risk activity for HBV transmission. Females have a significantly stronger adaptive immunity activation and viral elimination caused by higher level of immune cells, higher 17β-estradiol that mediate antiviral activity,[15] and anti-oxidant enzymes upregulation.[16] Therefore, HBeAg and HBsAg seronegativity are profound in females.[17]

Age and educational attainment have an unclear correlation with the disease. Patients in this study were dominantly aged 41 – 50 years old. Previous studies gained various results. Study at Dr. Pirngadi General Hospital[18] and Haji Adam Malik General Hospital Medan[19] were mostly aged >40 and 45 – 64 years old. This occurred due to different age intervals. Higher

incidence in elder patients can be related to the hepatitis B immunization program in Indonesia that started in 1997, thus, elder patients are at higher risk of not getting immunized.[20] A previous study showed a significant correlation between education and hepatitis B incidence in Beringin Primary Health Care, but not in Karangasem, Buleleng, and Negara Hospital.[21] These showed that complex factors contributed in HBV infection.

Decision on NA therapy considers individual condition. Therefore, different studies can give different results. This study showed that the majority of patients were consuming tenofovir, while patients at Dr. Sardjito General Hospital Yogyakarta were mostly consuming lamivudine.[13] According to clinical use, lamivudine is administered to HBeAg positive patients with ALT>2x ULT or histological status using AST Platelet Ratio Index (APRI) minimum at F2 stage and is lamivudine-sensitive based on clinical and laboratory results.[7,22] The study involved lamivudine-sensitive hospitalized patients with 88% successful response, only a patient changed to entecavir. Besides, lamivudine was cheaper and more available than other regimens in that setting. Tenofovir is recommended as the first line beside entecavir. Patient consuming tenofovir is higher achieving HBeAg seroconversion and undetectable HBV DNA.[23]

These study findings showed that NA group had significantly higher QoL in PCS and MCS. Limited previous studies showed various results. Studies in China[24] and Italy[25] supported the finding of PCS with several variables were also assessed for possible factors causing better QoL in NA group. Multivariate analysis indicated weakness as an independent predictor of PF, while sleep disorder decreases physical activity that reduces QoL. These two variables were less found in NA group.[25] On contrary, PCS was significantly higher in naïve group in a study in Turkey.[26] This can be explained by different population and criteria of the study. The study assessed Turkish patients with younger mean age. Age is negatively correlated with physical ability. A younger patient has higher physical ability and fitness compared with older patient because of higher muscle strength, agility, body fat composition, and endurance.[27] The study did not exclude other chronic comorbidities. Whereas, chronic comorbidities cause an increase in total chronic diseases suffered that potentially decreases QoL.[28]

BP projects bodily pain felt by patients. This study had insignificant higher score of BP in NA groups. Studies in China24 and Turkey[26] showed an insignificant higher score in NA and naïve group. Pain is affected by several physical, psychological, and environmental factors that are potential to cause differences in quality of pain felt. The most location of pain complained is anatomical liver position at the right upper quadrant of the abdomen.[29] Quality, progression, and duration of underlying disease are positively correlated with pain. Sociodemographic and socioeconomic characteristics contribute to pain. The elder is more vulnerable to chronic pain than the younger patient because of multi-morbidities which are caused by structural, functional, and biochemical changes. In daily life, routine physical exercise and good nutrition decrease pain, although with unclear mechanism and correlation. Yoga, aquatic, and aerobic exercises are most recommended to alleviate chronic pain. Besides, sunlight is suspected to decrease pain quality caused by less calcitriol produced that leads to anatomical, endocrine, neurological, and immunological changes, but this prediction needs to be reviewed further.[30]

MCS and the score of its subscales were significantly higher in NA group. Compared to previous studies, this was also higher significantly in Simonetti et al.[25] and insignificantly in Xue et al.[24] During data collection, many patients were anxious about their disease and repeated medical control. However, NA group had lower levels of anxiety, depression, altered concentration, and confusion.[25] Patients taking NA have higher confidence to cope with their disease, regardless of anxiety presentation.[26] Multivariate analysis showed anxiety as an independent predictor of social function, thus, fewer anxiety results in a higher SF mean score in NA group.[25] However, anxiety was also related to disease state. Difficulty in eradicating the virus from the body causes long-term infection that induces anxiety and depression because of the potency in progressive disease, complications, and death. Patients' knowledge about CHB is still limited and patients are also afraid of transmitting the virus to their family or partners.[31] According to that, it is crucial to give education about the disease, goals and effects of therapy, the importance to obey the instruction, involving the patient in decision making to increase patient confidence in CHB therapy and reduce anxiety.

Chronic inflammation as a biologic mechanism that affect QoL underlies the pathophysiology, which can be measured by using clinical parameters, such as elevated serum ALT, IL-6, and IL-8, a decrease of albumin level, and prolonged prothrombin time (PT). Serum ALT level increase is specifically projecting active hepatocytes damage and negatively correlated with QoL.[26] Liver damage causes disturbance of its function, including reduction of albumin and coagulation factors synthesis, thus altering homeostasis by disrupting intravascular osmotic pressure and prolonging PT. A study by Abdo showed the correlation between albumin and PF, RP, SF, BP, and GH.[32] The study also indicated a correlation of PT with SF and GH. Furthermore, high level of serum IL-6 decreases PF and MH, while IL-18 affects GH and SF.[33] However, the mechanism was poorly understood. NA suppresses inflammation by inhibiting HBV replication so that clinical parameters in patients consuming NA improved. In turn, QoL is expected to increase, thus enhancing the benefit of NA in hepatitis B therapy. Nevertheless, clinicians need to overcome the side effects so that NA can be comfortably taken by patients and increasing success rate of the medication.

Conclusion

Nucleoside analog treatment affected quality of life in CHB patients. Data showed significantly higher quality of life in physical components, including physical function, role limitation due to physical health, and general health perception, also in mental component, including role limitation due to emotional problems, vitality, emotional well-being, and social function compared to naïve patients. This result was approached due to nucleoside analog effect on inhibiting viral replication, thus preventing disease progression and improving mentality to face the disease.

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Conflict of Interest

The authors declare that they hold no competing interests.

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