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Antiviral therapy and prognostic analysis of chronic hepatitis B patients with HBsAg and anti-HBs co-existence

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Abstract: To investigate the prognosis of antiviral therapy in chronic hepatitis B patients with HBsAg and anti-HBs co-existence. Methods: Electrochemiluminescence immunoassay (ECLIA) was used to screen patients with HBsAg and anti-HBs co-existence (experimental group) and HBsAg-positive patients (control group) in patients with chronic hepatitis B. The levels of serum HBV DNA load, AFP and hepatic function before and after the administration of the drug were measured, the effect of antiviral therapy and the prognosis of patients were analyzed compared. Results: There was no significant difference in the age, gender and other basic indicators between the experimental group and the control group (P>0.05). In the experimental group, after the antiviral treatment, the HBV DNA load, AFP, and liver function were improved compared with baseline characteristics, and the difference was statistically significant (P<0.05). In the experimental group and the control group, the differences in HBV DNA load, AFP, and liver function levels before and after antiviral treatment were statistically significant (P<0.05). Conclusions: Antiviral treatment of patients with co-existent HBsAg and anti-HBs in chronic hepatitis B patients as well as antiviral treatment in patients with HBsAg-positive chronic hepatitis B has significantly improved their prognosis, but the prognosis of the former is slightly worse than that of the latter, patients are more likely to develop cirrhosis and even liver cancer, which should attract laboratory and clinical attention.

Keywords: Chronic hepatitis B; Hepatitis B surface antigen; Hepatitis B surface antibody; Antiviral therapy

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1.Introduction

If infected with hepatitis B virus (HBV), the hepatitis B virus surface antigen (HBsAg) persists for at least for 6 months and was still not cleared, it was called chronic HBV infection. This WHO Global Hepatitis Report (2017) estimates that in 2015, 257 million persons, or 3.5% of the population, were living with chronic HBV infection in the world. (HBV surface antigen-positive), and in china alone, more than 90 million persons are chronically infected with HBV, making China a hard-hit area for HBV infection[1]. In general, after exposure to HBV for 2 to 10 weeks, the body will produce HBsAg, and the appearance of anti-HBs indicates that the body is immune to HBV infection[2]. Since the first report of Arnold in 1976, chronic hepatitis B patients with co-existence HBsAg and anti-HBs have been reported more frequently[3, 4]. With the in-depth study, it has been reported that the simultaneous positive of HBsAg and anti-HBs may be related to the determinant mutation of HBV genotype C, the variation of "a" determinants, overlapping infections of different subtypes, and immune escape from viruses[5-9]. However, antiviral therapy and its prognosis in chronic hepatitis B patients with co-existence HBsAg and anti-HBs have rarely been reported.

At present, Interferon (IFN) and Nucleoside/Nucleotide (NUCs) analogues have been approved for the treatment of chronic HBV infection in China. The former includes common interferon (IFN-α), Peginterferon (PEG-IFN-α), a long-acting interferon,such as Pyrohim(PEG-IFN-α-2a, long-acting IFN-α covalently bound by a 40 kDa molecular weight polyethylene glycol and 1 IFNα-2a) and Pellet(PEG-IFN-α-2b, long-acting IFN-α covalently bound to IFN-α by a 12 kDa molecular weight polyethylene glycol). The latter include Lamivudine (LAM), Adefovir Divivoxil (ADV), Entecavir (ETV), Tenofovir (TDF), Telbivudine (LdT) , et al[10,11]. According to the Chinese Society of Liver Diseases and the Chinese Society of Infectious Diseases, all NUCs are recommended as preferred treatment medication for the treatment of chronic HBV infection[12], while the World Health Organization (WHO) and the American Association for the Study of Liver Diseases (AASLD) recommend ETVs and TDFs, which are not susceptible to drug resistance, be used as first-line NUCs drugs to treat chronic HBV infection[13,14]. According to the "Guidelines for Prevention and Treatment of Chronic Hepatitis B" issued by China, the indications for antiviral therapy for chronic HBV infection are: (1) HBV DNA ≥10E5 copies/m L (≥10E4 copies/mL for HBeAg negative); (2) ALT ≥2 × ULN (upper limit of normal value); if treated with interferon, ALT should be ≤ 10×ULN; (3) Liver histopathology has obvious inflammatory activity (G2-3) or moderate to high (S2) fibrotic lesions. Patients with (1) and (2) or (3), except for elevation of ALT caused by factors such as drugs or alcohol, should be treated with antiviral therapy. Those who fail to meet the above crite-

ria should be monitored for changes in their condition, If HBV DNA is persistently positive and ALT is abnormal, antiviral therapy should also be considered[15]. This study will investigate the prognosis of antiviral therapy in patients with chronic hepatitis B who are simultaneously positive for HBsAg and anti-HBs, and whether there is a difference in the prognosis of antiviral therapy in patients with HBsAg-positive chronic hepatitis B.

2.Materials and Methods

2.1 Subjects

The experimental group included 60 patients who were admitted to the inpatient department of the Third Affiliated Hospital of Sun Yat-sen University from January 2013 to June 2017. In the control group, 60 patients were enrolled in the inpatient department of the same Hospital from January 2016 to June 2017. Before the start of the experiment, both groups of patients were tested for serum HBV markers, using Roche Cobas e601 automatic electrochemiluminescence immunoassay analyzer and its supporting kits. All tests are carried out in strict accordance with the equipment and kit instructions, and according to the kit instructions, the normal reference standard value is set to: HBsAg ≤ 1COI (COI means cut-off index), anti-HBs ≤ 10 IU/L. All patients were initially screened, all met the diagnostic criteria for chronic hepatitis B, had not taken any antiviral drugs, or had previously taken antiviral drugs but had not taken it in the last six months. patients with hepatitis A, hepatitis C, hepatitis E, liver cancer, and HIV infection were excluded.

2.2 The inspection time

Before taking antiviral drugs, blood samples were taken from all patients for examination and analysis. After taking antiviral drugs, the patient was required to strictly follow the doctor's orders, insist on taking antiviral drugs without spontaneous discontinue. The time of serum HBV DNA load for the first review after taking the drug was the time for the follow-up examination.

2.3 Quantitative detection of serum HBV DNA

The HBV DNA load was measured using a fluorescent quantitative PCR kit(Da'an Gene Co. Ltd. of Sun Yat-sen University, china). When the HBV DNA load test result was >100 IU/ml, the load are reported according to the actual test results, and when the it was <100 IU/ml, they were reported as: "<100 IU/ml". For statistical analysis, for HBV DNA load >1.70E+08U/mL, it was expressed as 1.70E+08U/mL, and the for those <100IU/mL, it was expressed as 100IU/mL.

2.4 Quantitative detection of serum AFP

The Roche Cobas E601 automatic electrochemiluminescence immunoassay analyzer(Germany) and kit were used for the detection, and operated in strict accordance with instrument and kit instructions.

2.5 Detection of Liver Function Index

The serum ALT were detected by Hitachi 7600 automatic biochemical analyzer(Japan) and corresponding reagents, tests was carried out in strict accordance with the instrument and reagent instructions.

2.6 Statistical analysis

SPSS 20.0 software was used for statistical analysis. The K-S normality test was used to determine whether the data of each group satisfies the normal distribution. If the measurement data satisfies the normal distribution, it was described as mean ± standard deviation and paired t test was used for the determination of the difference within groups. Those who did not meet the normal distribution were described by the median and interquartile range. Paired non-parametric tests were used to evaluate intra-group differences. Count data are described by the number of cases and percent [n(%)], and the chi-square test was used to evaluate the differences between groups. Count data of multiple groups were compared by ANOVA. The difference between the experimental group and the control group after antiviral treatment was determined by independent sample t test or independent sample nonparametric test. $P<0.05$ was considered statistically significant.

3.Results

Comparison of antiviral treatment between HBsAg and anti-HBs co-existence patients and HBsAg positive patients

In the experimental group, 6 cases (10.00%)were treated with PEG-IFN-alpha-2a antiviral therapy, 5 cases (8.33%)were treated with PEG-IFN-alpha-2b antiviral therapy, 34 cases (56.67%)were treated with ETV antiviral therapy, TDF anti-virus treatment in 11 cases (18.33%),and LdT antiviral therapy in 4 cases(6.67%). In the control group, 5 cases (8.33%) were treated with PEG-IFN-alpha-2a antiviral therapy, 5 cases (8.33%) were treated with PEG-IFN-alpha-2b antiviral therapy, 31 cases (51.67%) were treated with ETV antiviral therapy, TDF antiviral therapy in 13 cases (21.67%), and LdT antiviral treatment in 6 cases (10.00%).

3.1Age and gender

The results are shown in Table 1. Using one-way analysis of variance (ANOVA), the ages of the two groups were comparable and there was no significant difference ($P>0.05$). After the chi-square test, the two groups were comparable in gender, with no significant difference ($P>0.05$).

3.2Serum HBV DNA load

The serum HBV DNA load levels of the experimental group and the control group before and after antiviral treatment were compared. The results are shown in

Table 2. The difference in serum HBV DNA load beforeTable 1 Patients Age and gender

		IFN		NUCs		
		PEG-IFN-α-2a	PEG-IFN-α-2b	ETV	TDF	LdT
age	case	29.33±4.45	24.80±4.55	42.25±13.77	51.00±13.17	47.35±12.17
	control	26.80±7.29	28.00±8.21	43.33±7.84	44.38±11.15	43.83±14.26
gender	case	4/2	3/2	25/9	9/2	3/1
（M/F）	control	3/2	3/2	24/7	11/2	4/2
P value	P	0.50	0.47	0.29	0.20	0.86
	P_1	0.82	1.00	0.72	0.86	0.78
	P_2					

Note: P1 for age and P2 for gender comparison between experimental group and

and after antiviral therapy (post-treatment load minus pre-treatment load) was compared between the experimental group and the control group for the prognosis of antiviral therapy. With independent t-test, when using PEG-IFN-α-2a, PEG-IFN-α-2b, and LdT for antiviral therapy, there was no significant difference between the two groups (P > 0.05), and when using ETV and TDF for antiviral therapy, the difference in prognosis was statistically significant (P<0.05).

Table 2 Serum HBV DNA load before and after antiviral treatment

HBV DNA load （log10 IU/mL）		IFN		NUCs		
		PEG-IFN-α-2a	PEG-IFN-α-2b	ETV	TDF	LdT
Case group	Before	6.95±1.06	6.09±1.18	6.74±1.32	6.45±1.09	7.03±1.39
	after	3.53±0.66	2.54±0.49	3.51±0.75	3.37±0.85	4.41±1.10
	difference	-3.41±0.47	-3.55±0.72	-3.24±0.92	-3.08±0.39	-2.63±0.52
Control	before	6.41±0.97	7.22±1.29	6.47±1.19	6.23±1.26	6.42±1.22
group	after	2.10±0.08	2.61±0,60	2.65±0.67	2.52±0.72	2.73±0.51
	difference	-4.31±0.96	-4.61±0.89	-3.82±0.89	-3.70±0.81	-3.68±0.88
P value		0.07	0.07	0.01	0.03	0.06

3.3Serum AFP before and after antiviral treatment

As shown in Table 3, the difference in serum AFP before and after antiviral therapy (post-treatment minus pre-treatment) was compared between the experimental group and the control group for the prognosis of antiviral therapy. When using PEG-IFN-α-2b and LdT for antiviral therapy, there was no significant difference before and after treatment (P>0.05) , compared with the independent t-test, However, when using PEG-IFN-α-2a, ETV, and TDF for antiviral therapy, there was a statistically significant difference of AFP between the two groups before and after treatment (P<0.05).

Table 3 Comparison of serum AFP levels before and after antiviral treatment

AFP（ng/mL）		IFN		NUCs		
		PEG-IFN-α-2a	PEG-IFN-α-2b	ETV	TDF	LdT
Case	Before	280.53±456.84	104.42±99.03	142.85±134.97	90,18±99.72	131.29±93.48
group	after	213.03±408.94	34.55±13.35	29.56(14.69,54.00)	69.58±65.12	84.77±44.92
	difference	-67.50±63.24	-69.87±107.20	-82.51±89.33	-20.60±48.55	-46.52±118.52
Control	before	288.62±201.67	89.92±71.84	206.12±254.10	155.39±142.72	82.84±80.37
group	after	22.43±19.63	6.31±3.03	25.01(7.18,34.18)	19.46(6.50,123.92)	22.52±14.15
	difference	-266.19±188.32	-83.61±71.44	-161.16±196.71	-91.19±92.83	-60.32±78.84
P value		0.04	0.82	0.04	0.03	0.83

3.4Serum ALT before and after antiviral treatment

The difference in serum ALT before and after antiviral therapy (post-treatment minus pre-treatment) was compared between the experimental group and the control group. Resuls were shown in Table 4. Compared with the independent t-test, when using PEG-IFN-α-2a, PEG-IFN-α-2b, TDF, and LdT for antiviral therapy, the difference was not statistically significant (P>0.05). When using ETV for antiviral therapy, however, there was a statistically significant difference of ALT between the two groups before and after treatment (P<0.05).

Table 4: Serum ALT before and after antiviral treatment

ALT（U/L）		IFN		NUCs		
		PEG-IFN-α-2a	PEG-IFN-α-2b	ETV	TDF	LdT
Case	Before	673.83±282.42	390.40±207.61	659.62±580.49	561.18±426.51	472.75±430.08
group	after	118.83±57.09	133.00±51.25	44.00(24.00,215.25)	246.36±34.42	107.75±59.54
	difference	-555.00±277.99	-257.40±179.67	-459.06±374.18	-314.82±302.45	-365.00±404.73
Control	before	583.80±463.10	541.80±409.50	820.26±624.29	458.31±367.83	470.83±356.23
group	after	55.60±27.33	92.00±100.09	54.00(35.00,98.00)	60.92±28.21	44.17±30.10
	difference	-528.20±441.06	-449.80±322.15	-713.51±544.31	-397.38±353.79	-426.67±360.22
Pvalue		0.90	0.29	0.03	0.55	0.81

Table 5: serological markers before and after antiviral treatment in patients with simultaneously positive HBsAg and anti-HBs

	HBV DNA Load（log10 IU/mL）	AFP（ng/mL）	ALT（U/L）
before	6.68±1.23	74.52(29.94,214.65)	608.10±509.27
After	3.47±0.83	33.00(21.27,99.44)	100.00(36.00,192.00)
P value	0.00	0.00	0.00

Differences in serological markers before and after antiviral treatment in patients with simultaneously positive HBsAg and anti-HBs

The difference before and after antiviral therapy in patients with HBsAg and anti-HBs co-existence were compared, and the results were shown in Table 5. According to paired t-test or paired non-parametric test, the difference before and after treatment was significant (P<0.05).

The prognosis of antiviral therapy in HBsAg and anti-HBs co-existent patients

When IFN was used for antiviral therapy, there was no significant difference in serum HBV DNA load, AFP and ALT before and after antiviral treatment between PEG-IFN-α-2a and PEG-IFN-α-2b treatment, the P values were 0.71, 0.91, 0.07, respectively, according to independent t test. When using NUCs for antiviral therapy, the differences in serum HBV DNA load, AFP, and ALT before and after antiviral therapy were compared by the independent t-test, and the difference was no statistically significant between ETV, TDF and LdT, the P values are 0.36, 0.11, 0.50, respectively.

4.Discussion

The overall goal of antiviral therapy for chronic hepatitis B includes maximized and long-termed suppression or elimination of HBV, reduce liver cell inflammation, necrosis and liver fibrosis, reduce and prevent liver decompensation, liver cirrhosis, hepatocellular carcinoma (HCC) and its complications, thereby delay the progression of the disease, prolonging survival and improving quality of life. Among them, continuous suppression of the virus is the key to reducing liver damage, therefore, antiviral treatment is the main content of chronic hepatitis B treatment. This study shows that antiviral therapy for patients with HBsAg and anti-HBs co-existent chronic hepatitis B is as effective as antiviral therapy for patients with HBsAg-positive chronic hepatitis B, which significantly improves the prognosis of patients, delay the progression of the disease and even prevent it from worsening and thus reach the therapeutic goal. As for the choice of antiviral drug treatment, there was no significant difference in the prognosis of patients (P>0.05). However, when deciding which drug to use, the patient's age, economic level, disease severity, history of liver disease, potential adverse reactions and complications, treatment compliance and patient's wishes must be taken

into account[15-17].

In this study, when PEG-IFN- alpha -2a, PEG-IFN- alpha -2b, TDF, and LdT were used for antiviral therapy, the difference of serum HBV DNA load level, serum AFP quantitative, and liver function indexes in chronic hepatitis B patients with simultaneous positive HBsAg and anti-HBs shown a certain degree of difference than that of HBsAg positive only chronic hepatitis B patients ($P>0.05$ or $P<0.05$). The reasons may be as follows: (1) the number of patients in the experimental group and the control group using PEG-IFN- alpha -2a, PEG-IFN- alpha -2b, TDF or LdT for antiviral treatment were relatively small. This may lead to unrepresentative results. The above results must be further studied when the number of cases reaches a certain statistical level. (2) The dropout rate in this study was high, the study did not provide long-term follow-up of the patient's prognosis, and thus the results of the study can only be partial. (3) Due to the reasons such as non-compliance of clinical drug use, there may be self-discontinuation leading to poor prognosis, even rebound and deterioration. (4) The mechanism of resistance to antiviral drugs varies from patient to patient, resulting in a possible emergence of resistance in individual patients after treatment. In the case of antiviral therapy using ETV, when the prognosis of patients with chronic hepatitis B who are both positive for HBsAg and anti-HBs compared with that of patients with chronic hepatitis B who are only HBsAg positive, there was a statistically significant difference in serum AFP and liver function ALT levels ($P<0.05$). Therefore, it is inferred that when the number of study cases is high, the prognosis of those groups of patients could be significant and may thus provides important clinical implications.

IFN treatment may stimulate the patient's immune system, and induce viral genome mutations to accelerate, NUCs treatment may also induce mutations in the overlapping linker S protein in viral reverse transcriptase. Some studies have reported that patients with simultaneously positive HBsAg and anti-HBs was in an immunosuppressed state[18,19]. The appearance of anti-HBs does not mean that HBsAg could be completely eliminated, and the recovery of hepatitis B can be achieved. Conversely, HBV DNA load in such patients could still be replicated[20], and even mutated, and is more likely to cause chronic damage to liver function[21]. In this study, serum HBV DNA load and liver function marker ALT after antiviral treatment in chronic hepatitis B patients with simultaneous positive HBsAg and anti-HBs were higher than those who were positive for HBsAg only, which is in consistent of the above reports. In addition, a long-term retrospective cohort study found that the incidence of hepatocellular carcinoma in the 5, 10, and 15 years of hepatitis B patients with co-existent HBsAg and anti-HBs was significantly higher than that of hepatitis B patients with HBsAg-positive alone[22]. It is believed that simultaneous positive HBsAg and anti-HBs increase the risk of developing liver cancer in chronic hepatitis B virus infection. Therefore, when antiviral treatment is performed, the prognosis of chronic hepatitis B patients who are both positive for HBsAg and anti-HBs is worse than that for chronic hepatitis B patients who are only HBsAg positive. Because the immune status of HBsAg and anti-HBs co-existent chronic hepatitis B patients may be in a suppressed state, When patients receive antiviral therapy, patient's condition should be more closely tracked and the relevant indicators of the response should be monitored, and if necessary, antiviral treatment regimen should be altered, stopped or chosen combined treatment.

In summary, antiviral therapy for patients with chronic hepatitis B is a long-term, difficult task that requires more in-depth research. Antiviral therapy for patients with chronic hepatitis B who are both positive for HBsAg and anti-HBs should be highly noticed by the laboratory and clinical researchers.

Author contributions

Mingliang Li designed the study and took responsibility for the integrity of data and the accuracy of the data analysis. Ling Yan contributed to data analysis, data interpretation, literature searches, and writing of the manuscript. Xiaofeng Yuan and Donglin Zhu contributed to data collection. All authors contributed to data acquisition, data analysis, or data interpretation, and reviewed and approved the final version.

Conflict of interest

The authors have declared that no conflict of interest exists.

References

[1]World Health Organization 2017, Global hepatitis report 2017.

[2]Pondé RAA. The underlying mechanisms for the "simultaneous HBsAg and anti-HBs serological profile". Eur J ClinMicrobiol Infect Dis. 2011;30:1325-40.

[3]Arnold W, Hess G, Meyer ZBK, et al. Simultaneous occurrence in the serum of hepatitis B surface antigen (HBsAg) and antibodies against HBsAg (Anti-HBs) of different subtypes. (Serologic and fluorescence histologic studies). Verh Dtsch Ges Inn Med. 1976;82:405-407.

[4]Shiels MT, Taswell HF, Czaja AJ, Nelson C, Swenke P. Frequency and significance of concurrent hepatitis B surface antigen and antibody in acute and chronic hepatitis B virus. Gastroenterology. 1987;93: 675-80.

[5]Liu Y, Zhang L, ZhouJY, et al.Clinical and Viro-

logical Characteristics of Chronic Hepatitis B Patients with Coexistence of HBsAg and Anti-HBs. PLoS One. 2016;11:e0146980.
[6]Liu W, Hu T, Wang X, et al. Coexistence of hepatitis B surface antigen and anti-HBs in Chinese chronic hepatitis B virus patients relating to genotype C and mutations in the S and P gene reverse transcriptase region. Arch Virol. 2012;157:627-634.
[7]Lada O, Benhamou Y, Poynard T, Thibault V. Coexistence of hepatitis B surface antigen (HBsAg) and anti-HBs antibodies in chronic hepatitis B virus carriers: influence of "a" determinant variants. J Virol. 2006;80:2968-75.
[8]Zhang JM, Xu Y, Wang XY, et al.Coexistence of hepatitis B surface antigen (HBsAg) and heterologous sub[9]type-specific antibodies to HBsAg among patients with chronic hepatitis B virus infection. Clin Infect Dis. 2007;44:1161-69.
[10]Ding F, Miao XL, Li YX, Dai JF, Yu HG. Mutations in the S gene and in the overlapping reverse transcriptase region in chronic hepatitis B Chinese patients with coexistence of HBsAg and anti-HBs. Braz J Infect Dis. 2016;20:1-7.
[11]Zheng X, Wang J, Yang D. Antiviral therapy for chornic hepatitis B in China. Med MicrobiolImmunol. 2015;204:115-20.
[12]Xing HC. Antiretroviral Therapy for Chronic Hepatitis B. Continuing Medical Education. 2006;20:12-21.
Chinese Society of Hepatology and Chinese Society of Infectious Diseases, Chinese Medical Association.[The guideline of prevention and treatment for chronic hepatitis B (2010 version). Zhonghua GanZangBing ZaZhi. 2011;19:13-24.
[13]Terrault NA, Bzowej NH, Chang KM, et al. AASLD guidelines for treatment of chronic hepatitis B. Hepatology. 2016;63:261-83.
[14]Park JW, Kwak KM, Kim SE, et al. Comparison of the long-term efficacy between entecavir and tenofovir in treatment--naïve chronic hepatitis B patients. BMC Gastroenterol. 2017;17:39.
[15]Chinese Society of Hepatology and Infectious Diseases. Guidelines for the prevention and treatment of chronic hepatitis B. 2015.
[16]Liaw Y-F, Leung N, Guan R, et al. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2005 update. Liver Int. 2005;25:472-89..
[17]LokaS, McMahon BJ. Chronic hepatitis B［M］. Alexandria（Va）: American association for the Study of Liver Diseases. 2004;25.
[18]Colson, P, Borentain P, Motte A, et al. Clinical and virological significance of the co-existence of HBsAg and anti-HBs antibodies in hepatitis B chronic carriers. Virology. 2007;367:30-40.
[19]Westhoff TH, Jochimsen F, Schmittel A, et al. Fatal hepatitis B virus reactivation by an escape mutant following rituximab therapy. Blood. 2003;102:1930.
[20]Zhu DL, Chen WS, Chen HP, et al. A follow-up study and analysis in patients with chronic hepatitis B and the coexistence of HBsAg and HBs. Chin J Health Lab Tec. 2016;26:1650-52.
[21]Zhang Y. Experimental analysis and reason discussion of patients with conrurrent HBsAg and HBsAb. Lab Med C lin. 2010;7:228-30.
[22]Seo SL, Choi HS, Choi BY, et al. Coexistence of hepatitis B surface antigen and antibody to hepatitis B surface may increase the risk of hepatocellular carcinoma in chronic hepatitis B virus infection: a retrospective cohort study. J Med Virol. 2014;86:124-30.