慢性HBV感染者经核苷(酸)类似物治疗获血清HBsAg转阴后的长期预后

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摘　要：【目的】回顾性研究长期服用核苷(酸)类似物的慢性乙型肝炎病毒(CHB)患者获得血清HBsAg转阴后的长期临床预后。【方法】选取中山大学附属第三医院长期服用核苷(酸)类似物抗病毒治疗获得血清HBsAg转阴的127例慢乙肝患者为研究对象，失访患者23例，纳入本研究的患者104例。定期收集患者临床数据，包括患者人口学数据、家族史、个人病史、基线及随访各时间点的生化学、病毒学、血清学、肝脾影像学指标以及药物治疗安全性数据等。【结果】104例患者中，85.6%(89例)男性，37.7%(34例)基线时HBeAg阳性；经过平均5.5(0.3～14.0)年核苷(酸)类似物治疗，HBsAg阴转时平均年龄为49.0(27.0～81.0)岁，ALT复常率为66.2 %(48/68)，HBV DNA不可测率为98.1 %(102例)，HBeAg转阴率为85.3 %(29/34)，HBeAg/HBeAb转换率为79.4 %(27/34)，HBsAg阴转率为100 %(104例)，HBsAg/HBsAb转换率7.7%(8例)。104例患者至最后1次随访时，ALT复常率为83.8 %(57/68)，HBV DNA不可测率为99.1 %(103)，HBeAg阴转率为88.2 %(30/34)，HBeAg/HBeAb转换率为79.4 %(27/34)，HBsAg阴转率为97.1 %(101)，HBsAg/HBsAb转换率为27.9%(29例)，3例患者出现HBsAg复转阳，但血清HBsAg滴度较低，HBsAg滴度对数值波动在-0.3～0.7 U/mL。1例(1.0%)患者从慢性乙型肝炎进展至肝硬化，2例(1.9%)肝硬化患者进展至肝癌，无1例患者死亡。【结论】服用核苷(酸)类似物抗病毒治疗的慢性HBV感染者获得血清HBsAg转阴后的长期临床预后良好。

关键词：慢性HBV感染者；血清HBsAg阴转；临床特点；长期预后
中图分类号：R51　　**文献标志码：**A　　**文章编号：**1672-3554(2018)06-0866-07

Long-Term Clinical Prognosis of CHB Patients with HBsAg Seroclearance after Long-Term Nucleos(t)ide Analogues Antiviral Therapy

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Abstract:【Objective】Retrospective study on the clinical characteristics and the long-term clinical outcome of regulatory follow-up chronic HBV infection patients achieving HBsAg seroclearance after long-term nucleos(t)ide analogues (NA) treatment.【Methods】127 chronic hepatitis B infection patients with HBsAg seroclearance after NA long-term treatment were selected as the study subjects, 23 patients loss of follow-up, and 104 patients were enrolled in the study. Routinely collected clinical data of the 104 patients with HBsAg seroclearance, including patient demographic data, family history, personal history, baseline and follow-up at each time point of biochemical, virological, serological response da-

收稿日期：2018-06-06
项目基金："十二五"重大科技专项(2012ZX10004-902)；广东省医学科学技术研究基金(2018366)
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ta, liver and spleen imaging indexes and drug safety during the treatment. Primary end point: HBsAg seroclearance rate (semi quantitative method: HBsAg titer < 1.0 COI; quantitative method: HBsAg titer < 0.05 U/mL). 【Results】In these patients who achieved serum HBsAg negative, 86.6% (89 cases) were male, 37.7% (34) were HBeAg positive at baseline. When HBsAg seroclearance after 5.5 (0.3-14.0) years follow-up, the mean age was 49.0 (27.0 ~ 81.0) years, ALT normalization was 66.2% (48/68) and HBV DNA undetectable rate was 98.1% (102/104), HBeAg seroclearance rate was 85.3% (29 / 34), HBeAg / HBeAb seroconversion rate was 79.4% (27/34), HBsAg/HBsAb seroconversion rate 7.7%(8/104). In the last follow-up, ALT normalization was 83.8% (57/68) and HBV DNA undetectable rate was 99.1% (103/104), HBeAg seroclearance rate was 88.2% (30/34), HBeAg / HBeAb seroconversion rate was 79.4% (27/ 34), HBsAg seroclearance rate was 97.1%(101/104), HBsAg/HBsAb seroconversion rate 27.9%(29/104). 3 cases in patients HBsAg turned positive again, but the level of lg HBsAg were very low, ranged from -0.3 to 0.7 U/mL. 3 patient developed disease progression to liver cirrhosis or liver cancer, and no one patient died. 【Conclusion】The long-term clinical prognosis of CHB patients with HBsAg seroclearance after long-term NA antiviral therapy was favourable.

Key word: chronic hepatitis B; HBsAg seroclearance; clinical characteristic; clinical outcomes

[J SUN Yat-sen Univ(Med Sci),2018,39(6):866-872]

乙型肝炎病毒(hepatitis B virus,HBV)长期持续慢性感染可能造成肝硬化、肝细胞癌等终末期肝病。核苷(酸)类似物(nucleos(t)ide analogues,NA)通过抑制HBV复制,降低慢性HBV感染者发生肝硬化、肝癌的发生率而广泛成为抗HBV治疗的一线药物。现阶段的研究显示,在慢性HBV感染人群中,血清乙型肝炎表面抗原(hepatitis B surface antigen,HBsAg)转阴的机率很低,每年仅1%左右[1-3]。但随着NA长期应用,临床上发生血清HBsAg转阴或清除的累积患者数量有逐渐增多的趋势。有报道显示,经过NA长期治疗的慢性HBV感染者每年血清HBsAg转阴或清除率波动在0.31%~4.1%[4-6]。血清HBsAg转阴或清除,代表着机体持久性的免疫控制,临床上接近治愈的状态。所以,本研究旨在通过对大队列服用NA抗病毒的慢性HBV感染者长期随访观察,探讨获得血清HBsAg转阴患者的基线特点,指标动态变化特点,对治疗应答的特点以及获得HBsAg转阴后的长期临床转归如何等,以便总结特点、发现规律,为核苷(酸)类似物治疗的有限疗程提供临床数据支持。

1　材料与方法

1.1　一般资料

自2006年1月至2015年12月中山大学附属第三医院随访门诊服用NA抗病毒治疗的慢性HBV感染者6715例,其中获得血清HBsAg转阴127例,剔除失访患者23例,本研究共纳入104例血清HBsAg转阴患者。104例获得血清HBsAg转阴的慢性HBV感染者一般情况见表1。慢性HBV感染者的诊断标准均符合2005年、2010年和2015年修订的《病毒性肝炎防治方案》[7-9]。

1.2　数据收集方法

收集服用NA抗病毒治疗的慢性HBV感染者的首次随访时、发生血清HBsAg转阴时、血清HBsAg转阴后第3月、6月、9月、1年、2年、3年、4年等的生化学指标(血清谷丙转氨酶,alanine amiotransferase, ALT; 血清白蛋白,serum albumin, ALB; 血清总胆红素,serum total bilirubin,TBIL; 血清肌酐,serum creatinine,Cr; 血清肌酸激酶,serum creatine kinase,CK)、病毒学指标(血清HBV DNA水平,最低检测值为100 U/mL)、血清学指标【乙型肝炎病毒表面抗原(surface antigen of HBV, HBsAg), 乙型肝炎病毒表面抗体(surface antibody of HBV,HBsAb),乙型肝炎病毒e抗原(e antigen of HBV,HBeAg),乙型肝炎病毒e抗体(e antibody of HBV,HBeAb),乙型肝炎病毒核心抗体(core antibody of HBV,HBcAb)】及临床安全性事件(如血钙降低、血磷降低、血清肌酸激酶升高、肾功能异常的发生率等情况,以及肝硬化、肝细胞癌发生率和死亡率)。

1.3　观察指标

主要终点指标:血清HBsAg转阴率;次要终点

表1 获得血清HBsAg转阴的慢性HBV感染者一般资料

Table 1 The basic characteristics of chronic HBV infection patients with HBsAg seroclearance after NA long-term treatment

[N = 104, %(n) or M(range)]

Item	Value
Gender	
Male	85.6(89)
Female	14.4(15)
Age/year	49.0(27-81)
Body mass index	23.2(15.4-32.7)
Family history	37.5(39)
Alcohol	26.0(27)
HBeAg positive	37.7(34)
Diagnosis	
Chronic hepatitis B	71.2(74)
Liver cirrhosis	3.8(4)
Hepatocellular carcinoma	25.0(26)
Duration of follow-up/year	5.8(0.5-15.4)
Duration of NA/year	5.5(0.3-14)
Initial NA treatment strategy	
Lamivudine	21.1(22)
Adefovir	26.0(27)
Telbivudine	18.3(19)
Entecavir	31.7(33)
Tenofovir	1.0(1)
Combination of lamivudine and adefovir	1.9(2)
Ratio of un-/changed therapy	65.4(68)/34.6(36)
Initial lamivudine	14.7(10)/33.3(12)
Initial adefovir	25.0(17)/27.8(10)
Initial telbivudine	19.1(13)/16.7(6)
Initial entecavir	36.8(25)/22.2(8)
Initial tenofovir	1.5(1)/0
Initial combination of lamivudine and adefovir	1.5(1)/2.8(1)
Unchanged/changed-therapy patients with EVR ratio	73.5(50)/36.1(13)
Duration of NA in patients with un-/changed therapy/year	5.2(0.6-9.5)/ 5.9(0.5-15.4)
Duration of HBsAg seroclearance in un-/changed patients/year	4.0(0.3-9)/ 6.6(0.5-14.0)
Number of changed strategy	1.3(1-3)

EVR: early virology response

指标:血清ALT复常率、血清HBeAg转阴率、血清HBeAg/HBeAb转换率。

1.4 统计学方法

采用SPSS 18.0软件进行数据统计分析。先对血清HBeAg水平、HBsAg水平、HBV DNA水平进行对数转换后再统计分析,计量资料以$\bar{x} \pm s$表示,非正态分布计量资料采用中位数(25%,75%四分位间距)表示;计数资料用百分比表示。

2 结 果

2.1 HBsAg转阴的慢性HBV感染者随访过程中各时间点各项指标动态变化情况

104例服用NA治疗获得血清HBsAg转阴的慢性HBV感染者经过长期临床随访观察发现,生化学、病毒学、血清学、影像学等各项指标均较基线有所改善,具体数值见表2;104例患者在获得血清HBsAg转阴时,仍分别有2例患者HBV DNA可测出、5例患者HBeAg呈阳性状态(表3);至最后一次随访时,104例获得血清HBsAg转阴的患者中,有3例患者出现血清HBsAg复转阳性(HBeAg阴性,表3)。

2.2 长期NA治疗获得血清HBsAg转阴的慢性HBV感染者长期临床结局

104例HBsAg转阴的慢性HBV感染者经过平均5.8(0.5~15.4)年的临床随访观察,预后良好(表4)。

3 讨 论

本研究通过分析104例长期服用NA获得血清HBsAg转阴慢性HBV感染者的临床特点及HBsAg阴转后长期转归发现,104例患者均为基线HBsAg水平较低,且对NA初始应答良好者。基线HBsAg对数的平均值为(2.8 ± 1.1)U/mL,服用NA期间发生初始病毒学应答者比例为60.6%(63/104)。

在之前本课题组对自然状态下发生HBsAg阴转或清除的患者分析中发现,基线HBsAg定量水平与HBsAg自发清除相关,也就是说基线HBsAg水平低的患者可能易于出现血清HBsAg转阴[11]。服用NA获得血清HBsAg阴转的患者同样也具备上述特点。另外有研究报道,使用核苷(酸)类似物过程中,血清HBsAg降低的速度及幅度可以预测HBsAg的清除。Brunetto等[12]研究发

表2　HBsAg转阴慢性HBV感染者在三个重要时间点生化学、病毒学、血清学、影像学指标的变化情况

Table 2　The biochemical, virological and serological value of different times in chronic HBV infection patients with HBsAg seroclearance after NA long-term treatment　[N = 104, $\bar{x} \pm s$ or %(n/N)]

Item	Baseline	Serum HBsAg loss	Last follow-up
ALT/(U/L)	91(40,211)	33.8 ± 23.1	30.3 ± 17.7
Alb /(g/L)	42.6 ± 5.4	45.3 ± 4.7	44.5 ± 4.9
Tbil /(μmol/L)	20.9(12.3,45.9)	19.0 ± 18.3	18.0 ± 17.0
ALT normalization rate[1)]	–	66.2(48/68)	83.8(57/68)
Level of lg HBV DNA /(U/mL)	5.2 ± 1.6	1.4 ± 0.9	1.2 ± 0.9
HBV DNA undetectable rate	–	98.1(102/104)	99.1(103/104)
HBeAg loss rate [2)]	–	85.3(29/34)	88.2(30/34)
HBeAg conversion rate[2)]	–	79.4(27/34)	79.4(27/34)
HBsAg loss rate	–	100(104/104)	97.1(101/104)
HBsAg conversion rate	–	7.7(8/104)	27.9(29/104)
Thickness of right liver/mm	116.7 ± 16.5	117.9 ± 12.0	114.1 ± 12.6
Width of portal vein/mm	11.5 ± 1.3	11.2 ± 0.9	11.2 ± 1.0
Thickness of spleen/mm	33.8 ± 8.1	33.8 ± 8.1	34.2 ± 5.7
Length of spleen/mm	103.4 ± 18.6	104.3 ± 17.5	105.8 ± 13.6
Width of spleen portal vein /mm	5.8 ± 1.7	5.6 ± 1.3	5.8 ± 0.7

1) N: the number of patients with ALT level elevation at baseline; n: the number of patients with ALT level normalization. 2) N: the number of patients with HBeAg positive at baseline; n: the number of patients with HBeAg negative conversion at each time point.

表3　HBsAg转阴时HBV DNA仍可测及HBeAg仍为阳性的慢性HBV感染者临床数据

Table 3　Clinical data of chronic hepatitis B patients with HBV DNA detectable or HBeAg positive when obtained serum HBsAg loss

Item	HBV DNA detectable when HBsAg loss (X_1, X_2)	HBeAg(+) when HBsAg loss [M(min,max)]	HBsAg(+) When last follow-up (X_1, X_2,X_3)
N(male)	2(2)	5(4)	3(3)
Age /years	(35,41)	32(24,37)	(23,25,36)
HBeAg (+) at baseline [%(n)]	100(2)	–	100(3)
ALT at baseline/(U/L)	(89,123)	161(83,42)	(86,323,97)
ALB at baseline/(g/L)	(43.1,45.6)	45.6(42.1,47.5)	(46.7,45.6,48.1)
TBIL at baseline /(μmol/L)	(12.3,15.7)	13.1(7.8,30.1)	(13.6,21.7,29.4)
lg HBV DNA at baseline /(U/mL)	(7.5,8.1)	6.7(5.2,7.7)	(6.7,8.1,6.9)
Duration of NA /years	(7.1,8.0)	6.1(4.6,7.9)	(6.3,5.7,6.7)
When HBsAg loss or last follow-up			
ALT when HBsAg loss/(U/L)	(21,25)	19(13,31)	(21,18,19)
ALB when HBsAg loss/(g/L)	(44.3,46.8)	46.0(43.2,48.2)	(46.9,46.2,47.8)
TBIL when HBsAg loss/(μmol/L)	(11.4,15.3)	11.2(9.3,16.4)	(12.1,13.7,13.3)
lg HBeAg when HBsAg loss/(U/mL)	–	0.10(0.03,0.13)	(−1.0,−0.5,−0.8)
lg HBV DNA when HBsAg loss/(U/mL)	(0.3,0.48)	Not Detected	Not Detected

表4 HBsAg转阴的慢性HBV感染者长期临床结局

Table 4 The long-term prognosis of chronic hepatitis B infection patients with HBsAg seroclearance after NA treatment [N = 104, %(n)]

Item	Value
Virologic breakthrough rate	0
HBsAg-positive reconversion rate	2.9(3)
HBsAg/HBsAb conversion rate	27.9(29)
Finite NA therapy	26.9(28)
Prognosis	
From CHB progress to Cirrhosis ratio	1.0(1)
From Cirrhosis progress to liver cancer ratio	1.9(2)
Death	0

现,使用拉米夫定对慢性HBV感染者抗病毒治疗到48周时,血清HBsAg滴度的对数值小于1 U/mL以及治疗到72周时血清HBsAg滴度的对数值降幅大于1 U/mL者与治疗结束3年后发生血清HBsAg阴转相关。遗憾的是,我们的研究因为随访时间跨度较大,因为科技水平的进步,血清HBsAg经历了半定量检测到定量检测的转变,但两种检测方法得到的结果之间无法进行换算,导致我们统计时无法计算HBsAg降幅。

针对血清HBsAg阴转或清除的慢性HBV感染者的长期临床转归,国内外也已经开展相似的研究,且研究证实,血清HBsAg阴转或消失接近临床治愈,代表HBV感染者的免疫控制,与良好的临床预后相关[13],可以实现安全停药或停药后不复发[14]。我们的研究也发现类似的结果。本研究中我们发现使用核苷(酸)类似物抗病毒治疗的104例发生血清HBsAg阴转的慢性HBV感染者中,有28例患者停用核苷(酸)类似物(其中20例患者系发生血清HBsAg阴转再巩固治疗一段时间后停药,但停药前未发生HBsAg/HBsAb血清学转换;8例患者系发生HBsAg/HBsAb血清学转换后停药),但无一例患者出现HBsAg复转阳及病毒学突破。

慢性乙型肝炎的治疗目标是通过长期持续抑制HBV DNA复制,从而实现血清HBsAg的清除。在大多数病例中,血清HBsAg转阴后肝组织和功能均得到改善[15]。然而,血清HBsAg的转阴并不总是意味着预后良好,获得血清HBsAg转阴后病情仍进展到肝硬化和更严重的肝功能失代偿的患者并不罕见。我们的研究也发现类似现象。本研究中我们发现,使用核苷(酸)抗病毒治疗过程中,即使发生血清HBsAg阴转,仍有3例患者出现病情进展,1例患者从基线时慢性乙型肝炎进展至乙肝肝硬化代偿期,2例失代偿期肝硬化患者进展至肝癌。Tang等[16]的研究也发现,35例血清HBsAg转阴患者中有4例发生肝细胞癌(2例为获得HBsAg/HBsAb转换的患者),HBsAg转阴和肝细胞癌发生的间隔分别为15, 16, 20和24个月。Ohba等[17]的研究也有慢性HBV感染者发生血清HBsAg转阴后仍发生肝细胞癌的报道。因此,乙肝肝硬化的患者即使在获得血清HBsAg转阴之后仍有可能进展为肝细胞癌。

Huang与Mahtab等[18-19]的研究发现获得血清HBV DNA和HBsAg转阴的慢性HBV感染者肝组织中仍能检测到HBV DNA;另一项研究发现[20],在30%至80%获得血清HBsAg转阴的肝癌患者的肿瘤组织中检测到HBV基因组。此外,HBV DNA的整合也可在获得血清HBsAg转阴肝癌患者的肝组织中发现[21]。HBV DNA可以通过整合到宿主细胞基因组或保持游离的游离体而持续存在于肝细胞中,整合本身可以通过激活其他癌症基因来触发致癌作用[22]。隐匿性病毒感染可在肝脏中产生轻度但持续的坏死性炎症,可引起细胞凋亡、坏死和代偿性再生的反复循环。所有这些在肝脏中的反应都有助于肝硬化和肝细胞癌的进展[23]。

血清HBsAg转阴患者发生肝细胞癌的其他因素还包括老年和HBsAg清除前存在肝硬化,以及HBsAg清除后持续的低白蛋白血症[15, 24]。本研究中有3例患者发生血清HBsAg阴转后仍出现疾病进展,可能与使用核苷(酸)类似物治疗人群中失代偿期肝硬化患者比例较大,以及与这3例患者年龄较大有关。

本研究结果可知,服用核苷(酸)类似物抗病毒治疗的慢性HBV感染者获得血清HBsAg转阴后的长期临床预后良好;对于HBsAg清除前发生肝硬化的患者,尤其是有肝癌家族史的患者,HBsAg清除后仍需要密切随访监测。

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(编辑 孙慧兰)

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(编辑 王晓鹰)