

· 病毒性肝炎 ·

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恩替卡韦与富马酸丙酚替诺福韦初治慢性乙型肝炎患者的肾功能变化比较及影响因素分析

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摘要: 目的 分析比较恩替卡韦(ETV)与富马酸丙酚替诺福韦(TAF)对初治慢性乙型肝炎(CHB)患者肾功能的影响。方法 回顾性分析2019年9月—2023年11月于南昌大学第一附属医院感染科门诊接受ETV或TAF治疗至少48周的167例初治CHB患者临床资料。根据患者抗病毒药物分为ETV组($n=117$)和TAF组($n=50$)。为均衡基线临床资料,采用倾向性评分匹配(PSM)按照2:1比例进行匹配分析,比较两组患者48周时肾小球滤过率(eGFR)水平及肾功能异常发生率。根据患者48周eGFR水平将患者分为肾功能正常组和异常组。计量资料两组间比较采用成组 t 检验或Mann-Whitney U 检验;计数资料组间比较采用 χ^2 检验或Fisher精确检验。采用多因素Logistic回归分析发生肾功能异常的影响因素,受试者工作特征曲线(ROC曲线)评估各指标预测发生肾功能异常的效能。采用Kaplan-Meier法分析肾功能异常累积发生率,并应用Log-rank检验进行比较。采用重复测量资料的方差分析比较CHB患者抗病毒治疗期间eGFR动态变化情况。结果 PSM成功匹配150例CHB患者,其中ETV组100例,TAF组50例。基线时,ETV组和TAF组一般资料比较,差异均无统计学意义(P 值均 >0.05),两组患者基线eGFR分别为(112.29 ± 9.92) $\text{mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ 和(114.72 ± 12.15) $\text{mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ 。48周时两组患者eGFR水平较基线均有下降,ETV组48周eGFR明显低于TAF组[(106.42 ± 14.12) $\text{mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ vs (112.25 ± 13.44) $\text{mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$, $t=-2.422$, $P=0.017$],肾功能异常发生率明显高于TAF组(17.00% vs 4.00%, $\chi^2=5.092$, $P=0.024$)。将患者分为肾功能正常组($n=131$)与异常组($n=19$)后,单因素分析结果显示,两组患者年龄($Z=-2.039$, $P=0.041$)、治疗药物(ETV/TAF) ($\chi^2=5.092$, $P=0.024$)、基线eGFR水平($t=4.023$, $P<0.001$)差异均有统计学意义;多因素Logistic回归分析显示,基线eGFR($OR=0.896$, 95% CI : 0.841 ~ 0.955, $P<0.001$)和治疗药物($OR=5.589$, 95% CI : 1.136 ~ 27.492, $P=0.034$)是发生肾功能异常的独立影响因素。基线eGFR预测CHB患者发生肾功能异常的ROC曲线下面积为0.781, cut-off值为105.24 $\text{mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$,敏感度和特异度分别为73.68%、82.44%。Kaplan-Meier曲线分析结果显示,基线eGFR $\leq 105.24 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ 组患者肾功能异常累积发生率高于基线eGFR $>105.24 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ 组患者($\chi^2=22.330$, $P<0.001$);ETV组患者肾功能异常累积发生率高于TAF组患者($\chi^2=4.961$, $P=0.026$)。随着抗病毒治疗启动,ETV组和TAF组患者eGFR均降低($F=5.259$, $P<0.001$),但仅在48周时ETV组eGFR水平明显低于TAF组($t=-2.422$, $P=0.017$);在基线eGFR $\leq 105.24 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ 和基线eGFR $>105.24 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ 的两组患者中,eGFR亦下降($F=5.712$, $P<0.001$),且基线及第12、24、36、48周两组患者eGFR比较,差异均有统计学意义(t 值分别为-13.927、-9.780、-8.835、-9.489、-8.953, P 值均 <0.001)。结论 对于ETV或TAF初治的CHB患者,ETV抗病毒治疗48周时的肾损伤风险高于TAF治疗。

关键词: 乙型肝炎, 慢性; 恩替卡韦; 富马酸丙酚替诺福韦; 肾损伤; 影响因素分析

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Changes in renal function in chronic hepatitis B patients treated initially with entecavir versus tenofovir alafenamide fumarate and related influencing factors

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Abstract: Objective To investigate the influence of entecavir (ETV) versus tenofovir alafenamide fumarate (TAF) on renal function in previously untreated patients with chronic hepatitis B (CHB). **Methods** A retrospective analysis was performed for the clinical data of 167 previously untreated CHB patients who received ETV or TAF treatment for at least 48 weeks at the outpatient service of Department of Infectious Diseases in The First Affiliated Hospital of Nanchang University from September 2019 to November 2023, and according to the antiviral drug used, they were divided into ETV group with 117 patients and TAF group with 50 patients. In order to balance baseline clinical data, propensity score matching (PSM) was used for matching and analysis at a ratio of 2:1, and the two groups were compared in terms of estimated glomerular filtration rate (eGFR) and the incidence rate of abnormal renal function at week 48. According to eGFR at week 48, the patients were divided into normal renal function group and abnormal renal function group. The independent-samples *t* test or the Mann-Whitney *U* test was used for comparison of continuous data between two groups, and the chi-square test or the Fisher's exact test was used for comparison of categorical data between two groups. The multivariate Logistic regression analysis was used to investigate the influencing factors for abnormal renal function, and the receiver operating characteristic (ROC) curve was used to assess the performance of each indicator in predicting abnormal renal function. The Kaplan-Meier method was used to analyze the cumulative incidence rate of abnormal renal function, and the log-rank test was used for comparison. The analysis of variance with repeated measures was used to compare the dynamic changes of eGFR during antiviral therapy in CHB patients. **Results** After PSM matching, there were 100 patients in the ETV group and 50 patients in the TAF group. There were no significant differences in baseline clinical data between the ETV group and the TAF group (all $P > 0.05$), with an eGFR level of 112.29 ± 9.92 mL/min/1.73 m² in the ETV group and 114.72 ± 12.15 mL/min/1.73 m² in the TAF group. There was a reduction in eGFR from baseline to week 48 in both groups, and compared with the TAF group at week 48, the ETV group had a significantly lower eGFR (106.42 ± 14.12 mL/min/1.73 m² vs 112.25 ± 13.44 mL/min/1.73 m², $t = -2.422$, $P = 0.017$) and a significantly higher incidence rate of abnormal renal function (17.00% vs 4.00%, $\chi^2 = 5.092$, $P = 0.024$). After the patients were divided into normal renal function group with 131 patients and abnormal renal function group with 19 patients, the univariate analysis showed that there were significant differences between the two groups in age ($Z = -2.039$, $P = 0.041$), treatment drug (ETV/TAF) ($\chi^2 = 5.092$, $P = 0.024$), and baseline eGFR level ($t = 4.023$, $P < 0.001$), and the multivariate Logistic regression analysis showed that baseline eGFR (odds ratio [OR] = 0.896, 95% confidence interval [CI]: 0.841—0.955, $P < 0.001$) and treatment drug (OR = 5.589, 95% CI: 1.136—27.492, $P = 0.034$) were independent influencing factors for abnormal renal function. Baseline eGFR had an area under the ROC curve of 0.781 in predicting abnormal renal function in CHB patients, with a cut-off value of 105.24 mL/min/1.73 m², a sensitivity of 73.68%, and a specificity of 82.44%. The Kaplan-Meier curve analysis showed that the patients with baseline eGFR ≤ 105.24 mL/min/1.73 m² had a significantly higher cumulative incidence rate of abnormal renal function than those with baseline eGFR > 105.24 mL/min/1.73 m² ($\chi^2 = 22.330$, $P < 0.001$), and the ETV group had a significantly higher cumulative incidence rate of abnormal renal function than the TAF group ($\chi^2 = 4.961$, $P = 0.026$). With the initiation of antiviral therapy, both the ETV group and the TAF group had a significant reduction in eGFR ($F = 5.259$, $P < 0.001$), but the ETV group only had a significant lower level of eGFR than the TAF group at week 48 ($t = -2.422$, $P = 0.017$); both the baseline eGFR ≤ 105.24 mL/min/1.73 m² group and the baseline eGFR > 105.24 mL/min/1.73 m² group had a significant reduction in eGFR ($F = 5.712$, $P < 0.001$), and there was a significant difference in eGFR between the two groups at baseline and weeks 12, 24, 36, and 48 ($t = -13.927$, -9.780 , -8.835 , -9.489 , and -8.953 , all $P < 0.001$). **Conclusion** For CHB patients initially treated with ETV or TAF, ETV antiviral therapy has a higher risk of renal injury than TAF therapy at week 48.

Key words: Hepatitis B, Chronic; Entecavir; Tenofovir Alafenamide; Kidney Injury; Root Cause Analysis

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HBV感染目前仍是全球重大公共卫生问题,据统计,全球有2.57亿人感染HBV,我国HBV感染者达7900万例,流行率为5.6%^[1]。目前抗病毒药物主要包括干扰

素和口服核苷(酸)类似物(NAs),因NAs具有较高的HBV DNA抑制率、高耐药屏障及安全性,故被推荐作为慢性乙型肝炎(CHB)患者的一线治疗药物,当前广泛使

用的NAs主要有恩替卡韦(ETV)、富马酸替诺福韦二吡呋酯(TDF)、富马酸丙酚替诺福韦(TAF)、艾米替诺福韦(TM5)等^[2-3]。其中TDF存在骨质疏松及肾功能损伤的风险,用药期间需定期监测血清肌酐(SCr)、肾小球滤过率(eGFR)、血磷等指标,建议存在肾损伤及骨质疏松风险的CHB患者改用ETV或TAF抗病毒治疗^[2,4-5]。然而,近期有研究^[6]显示,在使用ETV及TAF抗病毒的CHB患者中,ETV的肾损伤风险明显高于TAF。针对ETV和TAF两种药物,肾损伤风险是否存在明显差异,目前尚无定论。本研究通过观察ETV及TAF初治的CHB患者eGFR变化情况、肾功能异常发生率,比较两种药物的肾损伤风险,旨在为临床选择更优抗病毒治疗方案提供参考依据。

1 资料与方法

1.1 研究对象 选取2019年9月—2023年11月于本院感染科门诊就诊,ETV或TAF初治至少48周的CHB患者。观察截止时间为2023年11月30日。CHB的诊断标准符合《慢性乙型肝炎防治指南(2022年版)》^[2]。纳入标准:(1)接受ETV或TAF初治至少48周;(2)基线eGFR $\geq 90 \text{ mL}\cdot\text{min}^{-1}\cdot 1.73 \text{ m}^{-2}$;(3) ≥ 18 岁的成年人。排除标准:(1)合并其他类型的急、慢性肝炎患者(如甲型、丙型、丁型、戊型肝炎,自身免疫性肝炎,酒精性肝炎,药物性肝损伤);(2)合并失代偿期肝硬化的患者;(3)合并肾脏疾病、肾毒性药物使用史、高血压、糖尿病的患者;(4)合并恶性肿瘤、HIV感染的患者;(5)妊娠期患者;(6)资料不完整的患者。

1.2 研究方法 根据抗病毒治疗药物将患者分为ETV组和TAF组,为均衡基线资料,按2:1行倾向性评分匹配(PSM)。根据48周时患者eGFR $\geq 90 \text{ mL}\cdot\text{min}^{-1}\cdot 1.73 \text{ m}^{-2}$ 或 $< 90 \text{ mL}\cdot\text{min}^{-1}\cdot 1.73 \text{ m}^{-2}$ 进一步分为肾功能正常组和异常组。

1.3 观察指标 收集患者的一般资料,包括性别、年龄、身体质量指数(BMI)、有无肝硬化。实验室指标:基线及第12、24、36、48周患者高敏HBV DNA, HBsAg, HBeAg,血常规,肝、肾功能,血脂,血糖;eGFR(根据CKD-EPI计算)。影像学指标:腹部彩超、肝硬度测量(LSM)等。血常规、血生化指标均在本院检验科完成。高敏HBV DNA定量检测采用TaqMan实时荧光定量PCR(美国罗氏480实时荧光定量PCR仪),检测下限为20 IU/mL。血清HBV标志物采用美国雅培公司Abbott ARCHITECT仪器及试剂分析。

1.4 统计学方法 应用Rstudio按照最近邻配比法,将

ETV组和TAF组患者基线差异较大的指标进行PSM;采用SPSS 26.0和MedCalc 20.0软件进行统计学处理,GraphPad Prism 10软件进行绘图。正态分布的计量资料以 $\bar{x}\pm s$ 表示,两组间比较采用成组 t 检验;非正态分布的计量资料以 $M(P_{25}\sim P_{75})$ 表示,两组间比较采用Mann-Whitney U 检验。计数资料组间比较采用 χ^2 检验或Fisher精确检验。采用多因素Logistic回归分析CHB患者发生肾功能异常的独立影响因素,运用受试者工作特征曲线(ROC曲线)评估相关因素对患者发生肾功能异常的预测价值。采用Kaplan-Meier法分析肾功能异常累积发生率,并应用Log-rank检验进行比较。采用重复测量资料的方差分析比较eGFR动态变化情况。HBV DNA及HBsAg定量进行对数转换。 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 一般资料 共纳入167例CHB患者,通过PSM成功匹配150例,其中男89例(59.33%)、女61例(40.67%),年龄19~69岁,BMI平均 $(22.91\pm 3.24) \text{ kg/m}^2$ 。根据治疗药物分组,ETV组100例,男60例(60.00%)、女40例(40.00%);TAF组50例,男29例(58.00%)、女21例(42.00%)。两组患者治疗前一般资料比较,差异均无统计学意义(P 值均 >0.05)(表1)。

2.2 ETV组和TAF组CHB患者48周eGFR变化及肾功能异常发生率比较 48周时ETV组和TAF组患者eGFR较基线均有下降,ETV组48周时的eGFR水平明显低于TAF组($P<0.05$)。48周时两组患者共有19例发生肾功能异常(eGFR $< 90 \text{ mL}\cdot\text{min}^{-1}\cdot 1.73 \text{ m}^{-2}$),异常率为12.67%,其中ETV组有17例,异常率为17.00%,TAF组有2例,异常率为4.00%,两组eGFR异常率比较,差异有统计学意义($P<0.05$)(表2)。

2.3 CHB患者48周发生肾功能异常的影响因素分析 根据48周时eGFR水平,将150例CHB患者分为肾功能正常组131例(eGFR $\geq 90 \text{ mL}\cdot\text{min}^{-1}\cdot 1.73 \text{ m}^{-2}$)和肾功能异常组19例(eGFR $< 90 \text{ mL}\cdot\text{min}^{-1}\cdot 1.73 \text{ m}^{-2}$)。单因素分析结果显示,两组患者年龄、基线eGFR及治疗药物(ETV/TAF)比较,差异均有统计学意义(P 值均 <0.05)(表3)。将单因素分析中有统计学意义的指标纳入多因素Logistic回归分析,结果显示,基线eGFR($OR=0.896, 95\%CI: 0.841\sim 0.955, P<0.001$)、治疗药物(ETV/TAF)($OR=5.589, 95\%CI: 1.136\sim 27.492, P=0.034$)是CHB患者发生肾功能异常的独立影响因素。

表1 两组CHB患者PSM前后基线资料及特征比较

Table 1 Comparison of baseline clinical data and characteristics before and after propensity score matching in patients with chronic hepatitis B in the two groups

指标	匹配前			匹配后		
	ETV组(n=117)	TAF组(n=50)	P值	ETV组(n=100)	TAF组(n=50)	P值
年龄(岁)	35(30~44)	34(29~41)	0.239	35(30~44)	34(29~41)	0.435
男[例(%)]	72(61.54)	29(58.00)	0.668	60(60.00)	29(58.00)	0.814
BMI(kg/m ²)	22.86±3.21	22.76±3.53	0.855	22.98±3.10	22.76±3.53	0.698
HBV DNA(log ₁₀ IU/mL)	5.19(3.40~7.47)	5.04(3.59~7.69)	0.461	5.55(3.37~7.68)	5.04(3.59~7.69)	0.886
HBsAg(log ₁₀ IU/mL)	3.31(2.47~3.86)	3.68(2.82~4.32)	0.043	3.39(2.94~3.95)	3.68(2.82~4.32)	0.235
HBeAg阳性[例(%)]	53(45.30)	30(60.00)	0.082	51(51.00)	30(60.00)	0.297
TBil(μmol/L)	17.5(12.1~31.9)	15.0(12.0~34.4)	0.780	17.4(12.1~31.6)	15.0(12.0~34.4)	0.881
Alb(g/L)	44.8(40.3~47.4)	42.8(38.7~46.0)	0.063	44.8(39.6~47.2)	42.8(38.7~46.0)	0.100
ALT(U/L)	51.0(28.3~118.7)	64.6(25.9~112.9)	0.474	52.6(33.1~134.7)	64.6(25.9~112.9)	0.949
AST(U/L)	35.6(27.8~77.2)	42.0(26.2~90.3)	0.650	36.9(28.5~96.5)	42.0(26.2~90.3)	0.957
GGT(U/L)	29.0(16.2~58.0)	38.0(17.5~91.3)	0.237	29.3(17.0~59.0)	38.0(17.5~91.3)	0.384
ALP(U/L)	78.0(66.0~100.6)	82.5(63.1~100.9)	0.768	79.8(70.2~103.8)	82.5(63.1~100.9)	0.833
TG(mmol/L)	1.21(0.82~1.72)	1.13(0.79~1.70)	0.631	1.15(0.82~1.67)	1.13(0.79~1.70)	0.806
TC(mmol/L)	4.19(3.45~4.77)	4.63(3.70~5.46)	0.069	4.18(3.51~4.78)	4.63(3.70~5.46)	0.104
FBG(mmol/L)	4.97(4.61~5.34)	4.88(4.40~5.29)	0.403	5.00(4.61~5.40)	4.88(4.40~5.29)	0.348
SCr(μmol/L)	66.29±12.39	64.82±15.69	0.520	66.63±12.46	64.82±15.69	0.445
eGFR(mL·min ⁻¹ ·1.73 m ⁻²)	112.41±9.87	114.72±12.15	0.198	112.29±9.92	114.72±12.15	0.192
BUN(mmol/L)	4.10(3.50~4.90)	3.95(3.13~4.83)	0.164	4.10(3.50~4.90)	3.95(3.13~4.83)	0.173
Hb(g/L)	145(134~159)	143(131~155)	0.331	146(135~159)	143(131~155)	0.651
PLT(×10 ⁹ /L)	191±56	200±56	0.337	193±56	200±56	0.468
LSM(kPa)	7.1(6.1~10.3)	6.2(5.5~9.8)	0.113	7.1(6.1~10.3)	6.2(5.5~9.8)	0.105
肝硬化[例(%)]	10(8.55)	7(14.00)	0.286	8(8.00)	7(14.00)	0.248

注: TG, 甘油三酯; TC, 总胆固醇; FBG, 空腹血糖; BUN, 尿素氮。

表2 ETV组和TAF组患者48周临床资料比较

Table 2 Comparison of 48-week clinical data between patients in the ETV and TAF groups

指标	合计(n=150)	ETV组(n=100)	TAF组(n=50)	统计值	P值
HBV DNA 低于检测值下限[例(%)]	111(74.00)	73(73.00)	38(76.00)	$\chi^2=0.156$	0.693
HBsAg(log ₁₀ IU/mL)	3.24(2.84~3.59)	3.27(2.95~3.58)	3.18(2.59~3.66)	$Z=-1.196$	0.232
HBeAg阳性[例(%)]	68(45.33)	45(45.00)	23(46.00)	$\chi^2=0.013$	0.908
TBil(μmol/L)	14.5(11.0~17.9)	14.1(9.8~17.5)	15.3(12.0~19.7)	$Z=-1.718$	0.086
Alb(g/L)	45.5(43.3~47.3)	45.7(44.0~47.2)	44.5(42.3~47.7)	$Z=-0.833$	0.405
ALT(U/L)	23.5(16.9~31.8)	23.9(16.6~32.5)	23.4(18.0~34.7)	$Z=-0.419$	0.675
AST(U/L)	24.2(19.8~31.8)	25.3(19.6~31.9)	23.8(20.6~30.4)	$Z=-0.128$	0.898
GGT(U/L)	21.0(14.0~34.0)	21.7(15.0~34.0)	20.5(11.8~35.3)	$Z=-0.818$	0.414
ALP(U/L)	77.9(62.3~87.3)	77.4(62.8~88.7)	79.3(61.2~85.1)	$Z=-0.126$	0.900
TG(mmol/L)	1.22(0.95~1.70)	1.20(0.93~1.69)	1.23(0.95~1.75)	$Z=-0.413$	0.680
TC(mmol/L)	4.37(3.77~5.01)	4.37(3.80~5.00)	4.36(3.74~5.32)	$Z=-0.177$	0.859
FBG(mmol/L)	5.00(4.69~5.43)	4.95(4.64~5.45)	5.11(4.71~5.39)	$Z=-1.012$	0.311
SCr(μmol/L)	70.43±14.35	71.67±13.85	67.94±15.14	$t=1.506$	0.134
eGFR异常[例(%)]	19(12.67)	17(17.00)	2(4.00)	$\chi^2=5.092$	0.024
eGFR(mL·min ⁻¹ ·1.73 m ⁻²)	108.37±14.12	106.42±14.12	112.25±13.44	$t=-2.422$	0.017
BUN(mmol/L)	4.34±1.09	4.42±1.11	4.17±1.04	$t=1.334$	0.184
Hb(g/L)	146(135~158)	146(134~158)	147(135~159)	$Z=-0.036$	0.971
PLT(×10 ⁹ /L)	195±62	191±67	203±52	$t=1.224$	0.223
LSM(kPa)	6.7(5.6~8.4)	6.8(5.6~8.5)	6.5(5.6~7.9)	$Z=-0.706$	0.480
肝硬化[例(%)]	15(10.00)	10(10.00)	5(10.00)	$\chi^2=0.000$	>0.05

表3 肾功能正常组及异常组CHB患者基线临床资料及特征比较

Table 3 Comparison of baseline clinical data and characteristics between patients with normal and abnormal renal function in chronic hepatitis B groups

指标	合计(n=150)	肾功能正常组(n=131)	肾功能异常组(n=19)	统计值	P值
年龄(岁)	35(30~42)	34(29~41)	39(31~46)	Z=-2.039	0.041
男[例(%)]	89(59.33)	81(61.83)	8(42.11)	$\chi^2=2.676$	0.102
BMI(kg/m ²)	22.91±3.24	22.95±3.18	22.63±3.75	t=0.395	0.694
HBV DNA(log ₁₀ IU/mL)	5.54(3.52~7.67)	5.56(3.59~7.73)	5.29(2.96~7.45)	Z=-0.833	0.405
HBsAg(log ₁₀ IU/mL)	3.45(2.92~4.08)	3.40(2.93~4.24)	3.49(2.76~3.75)	Z=0.500	0.617
HBeAg阳性[例(%)]	81(54.00)	72(54.96)	9(47.37)	$\chi^2=0.385$	0.535
TBil(μmol/L)	16.8(12.0~31.8)	17.3(12.3~33.9)	13.8(9.0~24.7)	Z=-1.545	0.122
Alb(g/L)	44.0(39.3~47.1)	44.1(39.4~47.1)	43.9(36.7~46.4)	Z=-0.670	0.503
ALT(U/L)	54.0(32.0~129.5)	56.5(34.2~134.0)	38.8(24.4~103.0)	Z=-1.503	0.133
AST(U/L)	38.7(28.4~92.8)	39.3(28.5~95.0)	34.2(24.0~77.5)	Z=-1.011	0.312
GGT(U/L)	31.2(17.0~67.3)	32.0(18.0~75.0)	21.0(13.0~59.0)	Z=-1.427	0.154
ALP(U/L)	80.6(67.1~102.5)	80.9(67.5~103.0)	77.5(63.7~94.9)	Z=-0.848	0.397
TG(mmol/L)	1.14(0.81~1.69)	1.14(0.82~1.74)	1.03(0.74~1.48)	Z=1.043	0.297
TC(mmol/L)	4.35(3.55~5.08)	4.27(3.50~4.97)	4.50(3.98~5.41)	Z=-1.681	0.093
FBG(mmol/L)	4.99(4.48~5.36)	4.97(4.46~5.32)	5.00(4.52~5.43)	Z=-0.576	0.564
eGFR(mL·min ⁻¹ ·1.73 m ⁻²)	113.10±10.73	114.38±10.39	104.28±8.95	t=4.023	<0.001
Hb(g/L)	145(134~158)	144(135~157)	146(124~163)	Z=-0.249	0.804
PLT(×10 ⁹ /L)	195±56	197±55	181±62	t=1.177	0.241
LSM(kPa)	6.9(5.8~10.0)	6.9(5.7~10.0)	6.9(6.1~10.6)	Z=-0.774	0.439
肝硬化[例(%)]	15(10.00)	12(9.16)	3(15.79)		0.408
治疗药物[例(%)]				$\chi^2=5.092$	0.024
ETV	100(66.67)	83(63.36)	17(89.47)		
TAF	50(33.33)	48(36.64)	2(10.53)		

2.4 CHB患者发生肾功能异常影响因素的预测价值
为了评估患者肾功能异常发生的独立影响因素的预测效能,将上述Logistic回归分析提示的基线eGFR进一步行ROC曲线分析,结果显示,其预测CHB患者发生肾功能异常的ROC曲线下面积为0.781, cut-off值为105.24 mL·min⁻¹·1.73 m⁻²,敏感度和特异度分别为73.68%、82.44%(图1)。

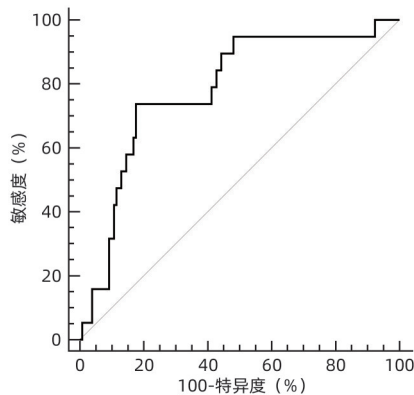
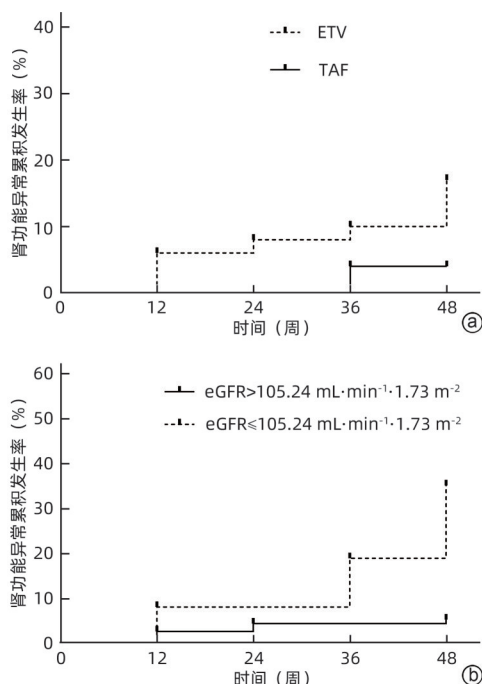


图1 基线eGFR预测CHB患者发生肾功能异常的ROC曲线
Figure 1 ROC curve for baseline eGFR predicting the occurrence of renal function abnormalities in CHB patients

2.5 不同治疗药物(ETV/TAF)和不同基线eGFR患者的肾功能异常累积发生率分析
通过Kaplan-Meier曲线分析不同治疗药物(ETV/TAF)CHB患者肾功能异常的累积发生率,结果显示,随着治疗时间的延长,两组患者肾功能异常发生率逐渐升高,且ETV组高于TAF组,差异有统计学意义($\chi^2=4.961, P=0.026$)(图2a)。

此外,根据基线eGFR水平将150例CHB患者分为基线eGFR>105.24 mL·min⁻¹·1.73 m⁻²组(113例)和基线eGFR≤105.24 mL·min⁻¹·1.73 m⁻²组(37例),Kaplan-Meier曲线分析结果显示,随着治疗时间的延长,两组患者肾功能异常发生率逐渐升高,但后者肾功能异常发生率高于前者,差异有统计学意义($\chi^2=22.330, P<0.001$)(图2b)。

2.6 不同治疗药物(ETV/TAF)、不同基线eGFR患者治疗期间eGFR动态变化分析
基线时,ETV组与TAF组患者的eGFR水平相当,差异无统计学意义($P>0.05$);随着抗病毒治疗启动,两组患者eGFR均降低($F=5.259, P<0.001$),比较各时间点两组患者eGFR水平差异,仅在48周时ETV组eGFR水平明显低于TAF组($t=-2.422, P=0.017$)(图3a)。



注:a,不同治疗药物患者肾功能异常累积发生率;b,不同基线eGFR患者肾功能异常累积发生率。

图2 不同分组的CHB患者肾功能异常累积发生率

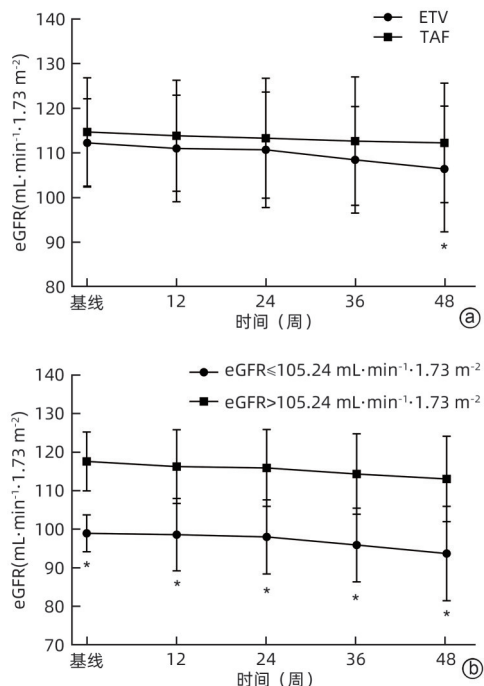
Figure 2 Cumulative incidence of renal function abnormalities in different groups of patients with chronic hepatitis B

随着对CHB患者抗病毒治疗的启动,基线eGFR $\leq 105.24 \text{ mL}\cdot\text{min}^{-1}\cdot 1.73 \text{ m}^{-2}$ 组和基线eGFR $>105.24 \text{ mL}\cdot\text{min}^{-1}\cdot 1.73 \text{ m}^{-2}$ 组患者eGFR均下降($F=5.712, P<0.001$),且各时间点两组患者eGFR比较,差异均有统计学意义(t 值分别为 $-13.927, -9.780, -8.835, -9.489, -8.953, P$ 值均 <0.001)(图3b)。

3 讨论

HBV感染可引起HBV相关性肾小球肾炎,导致肾损伤,是肾功能障碍的危险因素^[7-10]。真实世界研究^[11]表明,部分抗病毒治疗的CHB患者发生肾损伤的风险更高。因此,对于HBV感染者,尤其长期使用NAs抗病毒的CHB患者,应密切关注肾功能,选择肾毒性小、安全可靠的抗病毒药物至关重要。

目前广泛使用的口服抗病毒药物包括ETV、TDF、TAF、TMF,其主要通过肾脏排出,可通过损伤肾小管转运蛋白、线粒体毒性、细胞凋亡等途径导致肾功能障碍^[12-14]。TDF、TAF、TMF均是替诺福韦(TFV)的前体药, TDF在血液中很快水解为TFV,随血液循环经肾脏代谢,长期使用TDF可造成肾损伤。TAF和TMF以原型存在于血液循环中,在血浆中较TDF更稳定,且直接在肝细胞中



注:a,不同治疗药物患者各时间点eGFR水平;b,不同基线eGFR患者各时间点eGFR水平。* $P<0.05$ 。

图3 不同分组的CHB患者eGFR动态变化

Figure 3 Dynamic changes in eGFR in different groups of patients with chronic hepatitis B

被水解为TFV,并能更有效地将活性代谢物递送至肝细胞中,故在较低的药物剂量下细胞内的TFV水平较高,从而使TAF和TMF的肾损伤风险明显低于TDF^[15-18]。ETV以原型通过肾脏清除,肾脏安全性亦优于TDF^[10,19]。因此,ETV、TAF及TMF在肾损伤风险方面均低于TDF。欧洲肝病学会乙型肝炎指南^[4]建议,对于年龄 >60 岁, eGFR $<60 \text{ mL}\cdot\text{min}^{-1}\cdot 1.73 \text{ m}^{-2}$ 等有骨、肾损伤风险的人群,建议使用ETV或TAF抗病毒。美国肝病学会乙型肝炎指南^[5]建议,对于TDF引起的肾损伤及骨病,应停用TDF,换用ETV或TAF。我国《慢性乙型肝炎防治指南(2022年版)》^[2]建议,对于慢性肾脏病、肾功能不全或接受肾脏替代治疗的CHB患者,建议ETV或TAF抗病毒治疗。但关于ETV和TAF两种药物肾损伤风险的比较,目前尚无定论。

SCr和eGFR均为评估肾功能的指标。SCr是人体肌肉代谢产物,由肾小球滤过,随尿液排泄。eGFR是单位时间内两肾生成的超滤量,当肾功能受损时,SCr升高, eGFR下降。因SCr受性别、年龄等因素的影响,而eGFR的计算则考虑了上述相关因素的影响,所以使用eGFR评估肾功能更加准确^[20-21]。Peng等^[22]研究发现,在HBV相关慢加急性肝衰竭患者中,TAF的肾损伤风险明

显低于ETV。Jung等^[6]研究纳入298例初治的CHB患者,ETV组和TAF组各149例,平均随访时间近80周时发现,ETV组肾功能异常发生率高于TAF组,使用ETV抗病毒的肾损伤风险高于TAF。笔者团队前期研究^[23]表明,ETV经治的CHB患者序贯或联合TAF肾功能可得到改善。本研究分析比较了150例初治的CHB患者,发现48周时ETV组较TAF组患者eGFR下降更明显,ETV组较TAF组发生肾功能异常的比例更高(17.0% vs 4.0%),差异均有统计学意义(P 值均 <0.05),这与上述研究结果基本一致,提示在ETV或TAF初治的CHB患者中,长期使用ETV抗病毒治疗较TAF的肾损伤风险可能更高。此外,本研究中48周时两组患者的HBV DNA、HBsAg、ALT、AST与基线相比均有所下降,两组间差异均无统计学意义,提示ETV和TAF在病毒学应答及改善肝功能方面的疗效相当,与目前大多数研究结果^[24-25]相符。

关于肾功能异常的影响因素,有研究^[26-28]表明,性别、年龄、高血压、糖尿病、肝硬化、肥胖、血脂等是发生肾功能异常的独立影响因素。本研究根据48周时eGFR水平将患者分为肾功能正常组与异常组,发现基线eGFR、治疗药物(ETV/TAF)是发生肾功能异常的独立影响因素,与以上研究存在差异,原因在于:(1)本研究剔除了合并高血压、糖尿病的CHB患者;(2)eGFR的计算已纳入了性别及年龄因素。但本研究中肝硬化、BMI、血脂不是肾功能异常的独立影响因素,可能与本研究样本量较少有关。基线eGFR预测CHB患者发生肾功能异常的ROC曲线下面积为0.781,敏感度和特异度分别为73.68%、82.44%,cut-off值为 $105.24 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$,具有一定预测效能。进一步对CHB患者eGFR行动态分析发现,抗病毒治疗过程中eGFR下降,其中基线eGFR $\leq 105.24 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ 的患者更易发生肾功能损伤,原因可能是eGFR偏低的CHB患者药物清除更慢,更易出现药物蓄积,从而导致肾脏损伤^[29]。本研究还比较了ETV组和TAF组CHB患者抗病毒治疗期间eGFR变化,发现48周时ETV组患者eGFR明显低于TAF组,而基线时两组患者eGFR水平相当,由此可见,使用ETV抗病毒的肾毒性可能高于TAF治疗,对CHB患者在抗病毒治疗过程中监测eGFR的动态变化具有重要意义。此外,早期肾损伤常表现为肾小管功能异常,相关标志物包括尿 $\alpha 1$ 微球蛋白、 $\beta 2$ 微球蛋白和N-乙酰 β -D氨基葡萄糖苷酶等指标,有研究^[30]表明,ETV长期治疗CHB患者存在肾小管功能损伤的风险,本研究未纳入以上指

标,后期研究中将进一步比较两种药物在肾小管损伤风险方面的差异。

综上所述,本研究结果显示,ETV或TAF初治的CHB患者,ETV抗病毒治疗48周时的肾损伤风险高于TAF,长期ETV抗病毒治疗和基线eGFR水平是CHB患者48周发生肾功能异常的独立影响因素。此外,ETV和TAF在病毒学应答及改善肝功能方面的疗效相当。本研究为CHB患者选择抗病毒治疗方案提供了参考依据,但亦存在不足之处,一方面,未纳入评价肾小管损伤的相关标志物;另一方面,本研究为回顾性分析,可能存在样本量较少、随访时间较短等不足,后期有待多中心、前瞻性的大样本研究来进一步证实。

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