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文献综述 REVIEW

替诺福韦治疗慢性乙型肝炎进展

张 莉, 张福奎

张莉, 张福奎, 首都医科大学石景山教学医院 北京市石景山医院消化内科 北京市 100043

张莉, 副主任医师, 主要从事肝脏疾病的诊治与消化内镜下治疗等方向的研究.

作者贡献分布: 本文由张莉与张福奎共同完成.

通讯作者: 张莉, 副主任医师, 100043, 北京市石景山区石景山路24号, 首都医科大学石景山教学医院, 北京市石景山医院消化内科. wwwhhh9688@163.com
电话: 010-88429999

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Treatment of chronic hepatitis B with tenofovir

Li Zhang, Fu-Kui Zhang

Li Zhang, Fu-Kui Zhang, Department of Gastroenterology, Beijing Shijingshan Hospital, Capital Medical University, Beijing 100043, China

Correspondence to: Li Zhang, Associate Chief Physician, Department of Gastroenterology, Beijing Shijingshan Hospital, Capital Medical University, 24 Shijingshan Road, Shijiingshan District, Beijing 100043, China. wwwhhh9688@163.com

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Abstract

Tenofovir (TDF) is a potent hepatitis B virus (HBV) inhibitor with a high barrier to drug resistance, and it has been recommended as one of the first-line drugs to treat chronic hepatitis B (CHB). This paper reviews the recent advances in the treatment of CHB with TDF, especially in terms of its efficacy as first-line and second-line antiviral therapies as well as its role in the prevention of mother-to-child HBV transmission.

Key Words: Chronic hepatitis B; Antiviral therapy; Tenofovir; Nucleos(t)ide analogues

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摘要

替诺福韦(tenofovir, TDF)可快速强效抑制乙型肝炎病毒(hepatitis B virus, HBV)复制并且具有高耐药基因屏障, 被美国、欧洲和亚太等各大国际肝病学会和我国肝病学会指南推荐为治疗慢性乙型肝炎(chronic hepatitis B, CHB)的一线药物. 本文对TDF治疗CHB的研究进展, 特别是用于一线和二线抗病毒治疗的效果以及用于预防HBV母婴传播的作用进行综述.

关键词: 慢性乙型肝炎; 抗病毒治疗; 替诺福韦; 核苷(酸)类似物

核心提要: 替诺福韦作为慢性乙型肝炎患者的

背景资料
替诺福韦(tenofovir, TDF)可快速强效抑制乙型肝炎病毒(hepatitis B virus, HBV)复制, 并且具有高耐药基因屏障, 被世界卫生组织(World Health Organization, WHO)和美国、欧洲和亚太等各大国际肝病学会以及我国肝病学会指南推荐为治疗慢性乙型肝炎(chronic hepatitis B, CHB)的一线药物, 并且被WHO推荐为确诊或怀疑对其他核苷(酸)类似物耐药患者的二线药物.

同行评议者
李瀚旻, 教授, 主任医师, 湖北中医药大学附属医院; 张西波, 副教授, 副主任医师, 天津市南开医院肝胆胰外科

研发前沿

本文对应用TDF治疗CHB提供了新的证据, 诸如TDF作为CHB的一线药物和二线药物以及对特殊人群患者的效果, TDF用于预防HBV母婴传播的效果和安全性, TDF和聚乙二醇干扰素(PegIFN)-α联合治疗的应用前景等.

一线和二线抗病毒药物, 长期治疗的安全性良好, 可获得满意效果.

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0 引言

美国、欧洲和亚太等各大国际肝病学会和我国肝病学会指南均推荐, 慢性乙型肝炎(chronic hepatitis B, CHB)的治疗目的为持久抑制乙型肝炎病毒(hepatitis B virus, HBV)复制, 阻止疾病进展, 应用核苷(酸)类似物[nucleoside(acid) analogue, NA]治疗时, 应首选可快速强效抑制HBV复制并且具有高耐药基因屏障的恩替卡韦(entecavir, ETV)或替诺福韦(tenofovir, TDF)作为一线药物. 现对TDF治疗CHB的进展综述如下.

1 TDF用于CHB患者的一线治疗

2项III期研究[1]表明, 乙型肝炎e抗原(hepatitis B e antigen, HBeAg)阴性和阳性CHB患者应用TDF治疗48 wk时的病毒学应答(HBV DNA水平<69 IU/mL)率分别为93%和76%, 而应用阿德福韦酯(adefovir dipivoxil, ADV)治疗48 wk时的病毒学应答率分别仅为63%和13%(P<0.001), TDF治疗组HBeAg阳性患者的丙氨酸转氨酶(alanine aminotransferase, ALT)复常率为68%, 显著高于ADV治疗组的54%(P = 0.03), TDF治疗组的乙型肝炎表面抗原(hepatitis B surface antigen, HBsAg)转阴率为3%, 显著高于ADV治疗组的0%(P = 0.02). 应用TDF治疗3年时, HBeAg阴性和阳性患者的病毒学应答率分别为87%和72%, HBeA阳性患者的HBeAg转阴率为34%, HBsAg转阴率为8%[2]. 继续治疗至5年时, 患者的组织学改善(Knodell炎症坏死积分下降≥2分并且无纤维化加重)率为87%, 纤维化逆转(Ishak积分下降≥1U)率为51%, 基线肝硬化(Ishak积分为5或6U)患者的肝硬化逆转(积分下降≥1U)率为74%[3]. 基线时患有肝硬化并不影响TDF的抗病毒效果, 肝硬化和无肝硬化患者的病毒学应答率分别为99.2%和98.0%(P = 0.686), HBeAg阳性肝硬化和无肝硬化患者的HBsAg转阴率分别为14.4%和8.3%(P = 0.188)[4]. 应用TDF治疗7年时, 病毒学应答率高达99.3%, HBeAg阳性患者的HBeAg转阴率为54.5%, HBsAg转阴率为11.8%[5]. Fung等[6]研究表明, 基线高病毒载量(HBV DNA水平≥9 $\log_{10}$ copies/mL)的CHB患者应用TDF治疗, 也可获得满意的效果, 与基线病毒载量较低者相比, 治疗72-288 wk时的病毒学应答率相似.

两项研究[7,8]表明, 亚裔CHB患者应用TDF治疗48 wk和240 wk时的效果及安全性与非亚裔患者相似. 我国III期临床试验纳入509例HBV DNA水平≥10^5 copies/mL的CHB患者, 随机分组至应用TDF或ADV治疗, 48 wk时, TDF治疗组HBeAg阳性和阴性患者的病毒学应答(HBV DNA<400 copies/mL)率分别为76.7%和96.8%, 显著优于ADV治疗组(P<0.0001)[9].

美国一项研究[10]表明, 治疗依从性是影响CHB初治患者对TDF治疗应答的主要因素, 应用TDF治疗12和24 mo时, 患者依从性良好的累积比例分别为92.2%和83.1%, 累积病毒学突破率分别为4.8%和9.8%, 所有病毒学突破均与治疗依从性差有关.

TDF可用于治疗重症、接受免疫抑制治疗或肝移植等特殊人群CHB患者. 一项研究[11]纳入189例急性加重的重症CHB初治患者, 应用ETV或TDF治疗24 wk时, 两组患者的死亡或肝移植率、肝脏并发症发生率以及生化和病毒学应答率均相似.

Koskinas等[12]研究纳入38例接受免疫抑制剂的CHB患者, 包括25例应用TDF预防性治疗和13例HBV再激活应用TDF挽救治疗的患者, 均获得完全的生化和病毒学应答.

一项小样本研究[13]纳入乙肝肝硬化肝移植受者, 应用小剂量乙肝免疫球蛋白(hepatitis B immunoglobulin, HBIG)+TDF或ETV预防性治疗, 6 mo后停用HBIG, 继续单用TDF或ETV治疗, 随访中数时间为21 mo, 所有患者均维持HBsAg阴性和HBV DNA检测不出. 另外一项研究[14]纳入58例乙肝肝硬化肝移植受者, 应用HBIG±NA至少12 mo后, 停用HBIG, 继续应用TDF或ETV单药治疗, 所有患者均维持HBV DNA检测不出.

迄今为止, 尚无明确的TDF临床耐药报道. CHB患者应用TDF治疗7年, 未检测到TDF耐药发生[5].

2 TDF用于CHB患者的二线治疗

2015年WHO慢性HBV感染预防、关怀和治疗指南建议: 对于确诊或怀疑对拉米夫定(Lamivudine, LAM)、ETV、ADV或替比夫定(telbivudine, LdT)耐药(如有既往用药史或原发无应答)的患者, 推荐改用TDF, 对于ADV耐药者, 也可考虑改用ETV[15].

Yang等[16]研究纳入59例对LAM耐药, 换用LAM+ADV治疗至少6 mo后仍然应答欠佳的CHB患者, 随机分组至转换为TDF单药治疗或继续LAM+ADV治疗, 12、24、36和48 wk时, TDF治疗组患者的病毒学应答率分别为75.00%、82.14%、89.29%和96.43%, 均显著高于继续LAM+ADV联合治疗组(P<0.001). Fung等[17]研究表明, 对LAM耐药的CHB患者应用TDF治疗, 96 wk时的病毒学应答率为89.4%, 无TDF耐药发生. Lee等[18]研究纳入153例对LAM耐药的CHB患者, 应用TDF单药治疗(33例)或者TDF+LAM或TDF+LdT联合治疗(120例), 12 mo时, 两组患者的病毒学应答率相似. Park等[19]研究纳入80例对LAM耐药后加用ADV联合治疗获得部分应答的CHB患者, 应用TDF单药治疗或TDF+LAM联合治疗, 两组患者6 mo和12 mo时的病毒学应答率均无显著性差异. Cho等[20]研究纳入125例对LAM耐药, 换用ADV单药或联合治疗至少6 mo仍然应答欠佳的CHB患者, 转换至TDF单药治疗(18例)或基于TDF的联合治疗(107例), 48 wk时, 两组患者的病毒学应答率无显著性差异(P = 0.750), 之前对ADV无应答者和部分病毒学应答者的病毒学应答率也无显著性差异(P = 0.198). 一项荟萃分析[21]纳入5项研究, 总共包括683例对LAM耐药的CHB患者, 应用TDF单药治疗或基于TDF的联合治疗, 48 wk时的病毒学应答率和HBeAg转阴率均无显著性差异. 因此, 对LAM耐药的CHB患者, 换用TDF单药治疗, 即可获得满意的抗病毒效果.

Baran等[22]研究纳入对ADV应答不佳或耐药的CHB患者, 应用TDF治疗12、24和36 mo时, 32例对ADV应答不佳患者的病毒学应答率分别为75%、87%和94%, 28例ADV耐药患者的病毒学应答率分别仅为58%、79%和79%, ADV耐药为TDF不易获得病毒学应答的独立预测因素. 然而, Berg等[23]研究纳入ADV治疗96 wk应答不佳的患者, 给予TDF治疗168 wk时, 基线病毒载量以及对LAM和/或ADV耐药并不影响TDF的效果, 82%的患者可维持长期病毒学应答. Lim等[24]研究表明, 对ADV耐药、多药治疗失败的CHB患者, 应用TDF单药治疗与TDF+ETV联合治疗同样有效, 没有发生额外的耐药变异. 一项荟萃分析[25]纳入7项研究, 包括478例ADV经治CHB患者, 应用TDF单药治疗或基于TDF的联合治疗, 两组相比, 24、48和96 wk时的病毒学应答率以及48和96 wk时的HBeAg转阴率均无显著性差异. 因此, ADV经治患者换用TDF单药治疗, 可获得满意的抗病毒效果.

对ETV获得部分病毒学应答(PVR, 治疗48 wk时, HBV DNA水平自基线下降>2 $\log_{10}$ IU/mL, 但是应用PCR方法仍可检出)、治疗失败或耐药的CHB患者, 可加用TDF联合治疗或者转换至TDF单药治疗[26-28]. Chaung等[26]研究纳入86例对ETV获得PVR的CHB患者, 加用TDF联合治疗, 6、12和18 mo时的病毒学应答率分别为77.3%、86.4%和100%. Lu等[27]将ETV治疗获得PVR的患者转换至TDF单药治疗或ETV+TDF联合治疗, 6和12 mo时, 两组患者的病毒学应答率相似(均P>0.05). Lim等[28]纳入90例对ETV耐药的CHB患者, 应用TDF单药治疗或TDF+ETV(1.0 mg/d)联合治疗, 第48周时, 两组患者的病毒学应答率无显著性差异(71% *vs* 73%, P = 0.81), 自基线的平均HBV DNA水平下降也无显著性差异(3.65 $\log_{10}$ IU/mL *vs* 3.77 $\log_{10}$ IU/mL, P = 0.69), 无额外耐药变异发生.

多重耐药的CHB患者应用ETV+TDF联合治疗或TDF单药治疗, 也可获得满意的抗病毒效果[29-34]. Zoulim等[29]研究纳入92例对NA原发无应答、部分应答或发生病毒学突破的CHB患者, 58%存在单药耐药或多重耐药的证据, 转换至ETV(1.0 mg/d)+TDF联合治疗, 48 wk和96 wk时的病毒学应答率分别为76%和85%, 没有观察到治疗诱发的ETV或TDF耐药. Lee等[30]对93例多重耐药的CHB患者应用ETV+TDF联合治疗, 中数时间4.5 mo后, 74例患者(79.6%)获得病毒学应答, 基线HBV DNA水平较低, 而不是HBV耐药情况, 是获得病毒学应答的独立预测因素. Park等[31]研究纳入64例多重耐药的CHB患者, 应用ETV(1.0 mg/d)+TDF联合治疗48 wk时, 病毒学应答率为85.9%, 所有患者

创新盘点

CHB初治和经治患者, 包括多重耐药的NA经治患者, 均可应用TDF单药治疗, HBsAg水平可协助判断TDF的停药时机, TDF和PegIFN-α联合方案在提高HBsAg转阴率方面可能具有一定前景.

应用要点
各种类型的CHB患者, 包括多重耐药的NA经治患者, 应用TDF治疗均可获得满意的抗病毒效果.

未检出对TDF的耐药突变或新发突变. Liu等[32]研究纳入115例对应用2种或2种以上NA治疗、疗效欠佳的CHB患者, 转换至TDF单药治疗, 第12、24、48和72周时, 患者的病毒学应答率分别为57.4%、69.6%、74.8%和86.1%. Lee等[33]研究也表明, TDF单药治疗适用于多重耐药的CHB患者, 中数15 mo时, LAM耐药、LAM+ADV耐药和LAM+ETV耐药组患者的累积病毒学应答率分别为82.8%、81.4%和84.1%, 基线HBV DNA水平是获得病毒学应答的显著预测因素, 多重耐药对病毒学应答率并无影响. 一项荟萃分析[34]纳入9项研究, 包括1089例CHB患者, 对TDF单药治疗和基于TDF联合治疗的效果进行比较, 24、48和96 wk时, 两组患者的病毒学应答率无显著性差异(分别为62.5% *vs* 70.9%、78.1% *vs* 83.7%和86.4% *vs* 87.9%, *P*值分别为0.086、0.118和0.626), HBV DNA下降幅度、HBeAg转阴及血清学转换率均相似.

对LAM、ADV或ETV耐药或应答不佳等NA经治患者转换至TDF治疗, 均未检测到TDF耐药发生[17,23,24,28].

3 TDF用于阻断HBV母婴传播

TDF为FDA妊娠B类药物, 可作为妊娠期间CHB患者抗病毒治疗的首选.

我国台湾一项前瞻性多中心试验纳入118例高病毒载量(HBV DNA≥7.5 $\log_{10}$ IU/mL)的HBeAg阳性CHB孕妇, 其中62例于妊娠30-32 wk至产后1 mo应用TDF治疗, 对照组56例未应用抗病毒治疗, 分娩时, TDF组产妇的HBV DNA水平显著低于对照组[(4.29±0.93)$\log_{10}$ IU/mL *vs* (8.10±0.56)$\log_{10}$ IU/mL, *P*<0.0001], 新生儿的HBV DNA阳性率(6.15% *vs* 31.48%, *P* = 0.0003)以及婴儿6 mo时的HBsAg阳性率均显著较低(1.54% *vs* 10.71%, *P* = 0.0481), 多变量分析表明, 孕妇应用TDF治疗, 可显著降低婴儿6 mo时的HBsAg阳性风险(OR = 0.10, *P* = 0.0434). 两组相比, 孕妇的肌酐、肌酸激酶水平以及婴儿的先天性异常发生率、早产率和生长参数均相似[35].

Pan等[36]牵头的中国HBV母婴传播研究纳入200例HBeAg阳性、HBV DNA水平>200000 IU/mL的孕妇, 以1∶1的比例随机分组, 不应用抗病毒治疗, 或者于妊娠30-32 wk至产后4 wk, 应用TDF治疗, 随访至产后28 wk, 所有婴儿接受免疫预防. 分娩时, TDF组和对照组孕妇相比, 有更高的比例达到HBV DNA水平<200000 IU/mL(68% *vs* 2%, *P*<0.001), 产后28 wk时, TDF组的HBV母婴传播率显著低于对照组(意向性治疗分析: 5% *vs* 18%, *P* = 0.007; 按方案分析: 0% *vs* 7%, *P* = 0.01). 两组母亲和婴儿的安全性相似, 停用TDF后, 两组母亲的HBV血清学转归无显著性差异.

4 TDF治疗的停药时机

CHB患者停用NA后的复发率较高. Fong等[37]对54例HBeAg阳性CHB患者应用ETV或TDF治疗, 达到HBeAg血清学转换并且巩固治疗后停药随访, 仅有4例(7%)患者可维持病毒学、血清学和生化应答. Chi等[38]研究纳入94例HBeAg阳性或阴性患者, 应用NA≥1年停药时, 均为HBeAg阴性, HBV DNA检测不出. 停药后第3年时, 基线HBeAg阳性和阴性患者的病毒学复发率分别为49%和53%. 巩固治疗≥3年与持续病毒学复发率较低有关, 并且可提高HBsAg转阴的可能性. Jeng等[39]研究表明, HBeAg阴性患者停用TDF治疗后, 临床复发通常发生于停药6 mo之内, 1年累积复发率为52%, 治疗持续时间>3年, 并且巩固治疗时间>2年, 可使临床复发率降低至30%.

应用TDF治疗期间或停药后的HBsAg水平变化, 有助于预测病毒学应答. Marcellin等[40]研究表明, HBeAg阳性CHB患者应用TDF治疗后获得HBsAg转阴的最强预测因素包括: 白种人感染基因A/D型病毒、感染时间≤4年和治疗24 wk时的HBsAg水平下降≥1 $\log_{10}$ IU/mL(HR = 13.7, 95%CI: 5.6-33.7, *P*<0.0001). Buti等[41]对8例HBeAg阴性CHB患者应用TDF治疗超过7年, 持续抑制病毒复制后停药, 全程接种HBV疫苗, 随访72 wk, 5例患者获得持续应答(HBV DNA水平<2000 IU/mL且ALT正常), 1例患者获得HBsAg转阴, 2例患者需要再治疗. 治疗期间HBsAg水平下降>5000 IU/mL以及停药后ALT波动期间, HBsAg水平<100 IU/mL的患者均获得持续应答.

5 TDF和聚乙二醇干扰素联合/序贯方案

应用NA治疗CHB的疗程相对不固定, HBeAg血清学转换率较低, 极少获得HBsAg转阴.

对于获得HBeAg血清学转换和HBsAg转阴, NA和聚乙二醇干扰素(polyethylene glycol interferon, PegIFN)-α联合或序贯方案可能具有一定优势.

Marcellin等[42]研究纳入740例CHB患者, 随机分组至TDF+PegIFN-α-2a联合治疗48 wk(A组)、TDF+PegIFN-α-2a联合治疗16 wk后, TDF单药治疗32 wk(B组)、TDF单药治疗120 wk(C组)或PegIFN-α-2a单药治疗48 wk(D组), 72 wk时, 四组患者的HBsAg转阴率分别为9.1%、2.8%、0.0%和2.8%, A组的HBsAg转阴率显著高于C组(P<0.001)或D组(P = 0.003), 而B组的HBsAg转阴率与C组(P = 0.466)或D组无显著性差异(P = 0.883).

在应用PegIFN-α治疗之前, 需要应用血清学指标和/或瞬时弹性成像等检测方法, 必要时进行肝活检, 除外进展期肝纤维化或肝硬化患者. 需要进一步研究, 确定有助于获得HBeAg血清学转换和HBsAg转阴的最佳联合或序贯治疗方案.

6 长期应用TDF治疗的安全性良好

多数CHB患者需要长期应用NA治疗, 所以, 其安全性至关重要. 对真实世界中CHB患者应用TDF治疗的安全性证据进行综述表明, 患者的耐受性良好, 没有发生临床显著的肾脏毒性. 一些研究报告了TDF相关的肾功能损害, 然而, 来自队列研究的证据并不一致. 不同研究中, TDF治疗与肾功能指标变化的关联程度各不相同, 可能是由于应用不同的定义和阈值报告肾毒性以及患者人群的差异所致[43].

CHB患者应用TDF治疗7年临床研究的开放标签期间, 血清肌酐水平较基线升高≥0.5 mg/dL的患者比例仅为1.7%[5]. Tsai等[44]对170例CHB患者应用TDF治疗平均17 mo后, 估算的肾小球滤过率(estimated glomerular filtration rat, eGFR)由92.2 mL/min每1.73 m^2降低至85.6 mL/min每1.73 m^2(P<0.001). 多变量分析表明, 之前存在肾功能不全(P = 0.003)、应用TDF(P = 0.007)和应用利尿剂(P = 0.001)是发生肾功能减退的独立预测因素. Maggi等[45]研究纳入60例应用LAM+ADV联合治疗转换至TDF治疗的CHB患者, 基线eGFR为89.3 mL/min±19.0 每1.73 m^2, 转换至TDF单药治疗6 mo时, eGFR有所下降, 之后保持稳定. Wang等[46]研究表明, CHB患者应用TDF治疗12 mo之内, eGFR有所降低, 然而, 继续治疗至13-36 mo期间, eGFR未再进一步显著降低. 患有糖尿病是肌酐水平较基线升高≥0.5 mg/dL的独立预测因素, 年龄、高血压、糖尿病和基线肌酐水平是eGFR较基线下降>20%的独立预测因素. 然而, Ha等[47]研究纳入103例应用TDF治疗和103例应用ETV治疗的匹配患者, 对性别、年龄、基线高血压、糖尿病、肾功能受损和肝硬化进行校正后, Cox比例风险分析表明, 应用TDF治疗并非肾功能显著恶化的独立预测因素. Patricio等[48]研究表明, 32例CHB患者应用TDF治疗1年后, eGFR和尿液胱抑素C、β2-微球蛋白和中性粒细胞明胶酶相关脂质运载蛋白均无显著性变化, 而甲状旁腺素水平显著升高(P = 0.012). Rodríguez-Nóvoa等[49]研究纳入280例CHB患者, 包括ETV治疗组89例、TDF治疗组69例和对照组122例患者, TDF组有25%的患者发生视黄醇结合蛋白(retinol-binding protein, RBP)/肌酐水平变化, 显著高于ETV和对照组7%的患者比例(P<0.001), 多变量分析表明, 应用TDF治疗与RBP/肌酐排泄改变风险增加独立相关(P = 0.013), 表明TDF治疗可能导致亚临床肾小管损伤. 因此, CHB患者应用TDF治疗之前和期间, 需要对eGFR和血磷等指标进行监测, 必要时, 及时进行剂量调整或换药.

CHB患者应用TDF治疗第4-7年期间, 骨密度(bone mineral density, BMD)无显著变化[5]. Maggi等[45]研究纳入60例应用LAM+ADV联合治疗转换至TDF治疗的CHB患者, 基线BMD轻度降低, 转换至TDF治疗12 mo时, 基线时的BMD降低无进一步加重. Gill等[50]研究表明, 高龄、吸烟、体质量指数较低和应用TDF治疗是CHB患者BMD降低的独立预测因素.

7 肝细胞癌的监测

Kim等[51]对参与TDF关键注册研究的患者随访384 wk, 无肝硬化和肝硬化患者的每年肝细胞癌(hepatocellular carcinoma, HCC)发生率分别为0.28%和0.65%. 在基线时无肝硬化的患者中, 观察到的HCC发生率显著低于应用CHB患者HCC风险评估(REACH-B)模型所预测的HCC发生率(SIR = 0.40, 95%CI: 0.199-0.795), 基线肝硬化患者的HCC发生率也有降低趋势(SIR = 0.51, 95%CI: 0.231-1.144). Coffin等[52]

同行评价

TDF治疗CHB进展的相关论文较多, 但本文主要是探讨用于一线和二线抗病毒治疗的效果以及用于预防HBV母婴传播的作用进行综述, 具有一定的学术指导价值.

研究纳入549例应用NA治疗的CHB患者, 其中41%应用TDF治疗, 中数随访时间为3.2年时, 11例患者(3.2%)诊断为HCC. 观察到的每年HCC发生率(0.9%, 95%CI: 0.5-1.7)显著低于通过REACH-B模型计算的预测发生率(SIR = 0.46, 95%CI: 0.23-0.82).

Papatheodoridis等[53]研究纳入1666例应用ETV或TDF治疗的白人CHB患者, 无肝硬化、代偿期肝硬化和失代偿期肝硬化的患者比例分别为67%、39%和3%, 开始ETV或TDF治疗1年、3年和5年时的累积HCC发生率分别为1.3%、3.4%和8.7%, 高龄和血小板减少是HCC发生风险的独立预测因素, 多变量分析表明, 利用亚洲患者数据建立的REACH-B等各种预测模型评分与HCC发生风险并无相关. 另外一项多中心研究[54]纳入1815例应用ETV或TDF治疗≥12 mo的白人CHB患者, 根据基线时的患者年龄、性别和血小板计数, 建立PAGE-B评分, 可以准确预测ETV或TDF治疗5年的HCC风险.

总之, CHB的治疗目的为持久抑制HBV复制和阻止疾病进展, 应用NA治疗时, 应首选高耐药基因屏障的ETV或TDF作为一线药物, 其中, TDF可快速强效抑制HBV复制, 并且具有高耐药基因屏障, 尤其对于NA经治患者, TDF是抗病毒治疗的首选用药.

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