doi: 10.13241/j.cnki.pmb.2021.10.029

替诺福韦联合聚乙二醇干扰素α-2b注射液对慢性乙型肝炎患者HBe Ag血清学转换率和阴转率的影响*

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摘要 目的：探讨替诺福韦联合聚乙二醇干扰素α-2b注射液对慢性乙型肝炎患者HBe Ag血清学转换率和阴转率的影响。**方法：**2018年2月到2020年8月选择在我院联合汀州医院诊治的慢性乙型肝炎患者104例，根据随机数字表法把患者分为联合组与对照组各52例。对照组给予聚乙二醇干扰素α-2b注射液治疗，联合组给予替诺福韦联合聚乙二醇干扰素α-2b注射液治疗，两组都治疗观察48 w。对比两组治疗前后患者的HBeAg血清学转换情况及HBV-DNA的转阴情况，血清谷丙转氨酶(Alanine transaminase，ALT)、谷草转氨酶(Aspartate transaminase，AST)含量。**结果：**治疗后联合组的HBe Ag血清学转换率为11.54 %，高于对照组的3.85 %(P>0.05)。治疗后联合组的HBV DNA转阴率为100 %，高于对照组的71.17 %(P<0.05)。两组治疗后的血清ALT与AST值低于治疗前(P<0.05)，联合组低于对照组(P<0.05)。**结论：**替诺福韦联合聚乙二醇干扰素α-2b注射液对慢性乙型肝炎患者能提高HBe Ag血清学转换率和阴转率，改善患者的肝功能。

关键词：替诺福韦；聚乙二醇干扰素α-2b；慢性乙型肝炎；血清学转换率；阴转率
中图分类号：R512.62 **文献标识码：**A **文章编号：**1673-6273(2021)10-1938-04

The Effect of Tenofovir Combined with Peginterferon α-2b Injection on HBe Ag Seroconversion Rate and Negative Conversion Rate in Patients with Chronic Hepatitis B*

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ABSTRACT Objective: To investigate the effect of tenofovir combined with peginterferon α-2b injection on HBe Ag seroconversion rate and negative conversion rate in patients with chronic hepatitis B. **Methods:** From February 2018 to August 2020, 104 cases patients with chronic hepatitis B who were diagnosed and treated in our hospital and Tingzhou hospital were selected as the research objects. All the cases were divided into combination group and a control group with 52 cases each groups accorded to the random number table method. The control group were treated with peginterferon α-2b injection, and the combination group were treated with tenofovir combined with peginterferon α-2b injection. Two groups were treated for 48 weeks. Compare the HBeAg seroconversion and HBV DNA conversion of the patients before and after the correct treatment, and the serum alanine aminotransferase (alanine aminotransferase, ALT) and aspartate aminotransferase (aspartate aminotransferase, AST) levels of the patients. **Results:** After treatment, the HBe Ag seroconversion rate of the combined group was 11.54 %, which was higher than that of the control group of 3.85 %, but the comparison was not statistically significant (P>0.05). After treatment, the negative rate of HBV DNA in the combined group was 100 %, which was higher than 71.17 % in the control group (P<0.05). The serum ALT and AST values of the two groups after treatment were lower than before treatment (P<0.05), and the combination group were lower than the control group (P<0.05). **Conclusion:** Tenofovir combined with peginterferon α-2b injection can increase the seroconversion rate and negative conversion rate of HBe Ag in patients with chronic hepatitis B, and improve the liver function of patients.

Key words: Tenofovir; Peginterferon alpha-2b; Chronic hepatitis B; Seroconversion rate; Negative conversion rate
Chinese Library Classification(CLC): R512.62 Document code: A
Article ID: 1673-6273(2021)10-1938-04

* 基金项目：福建省自然科学基金项目(2018J0547)
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(收稿日期：2020-12-02 接受日期：2020-12-24)

前言

慢性乙型肝炎是由于乙型肝炎病毒(HBV)感染发展而来的慢性肝脏疾病之一，也是发病率较高的慢性传染性疾病之一，具有治愈难度大、病程长、易复发等特点[1,2]。随着病情的进展，该病可进展到肝硬化与肝癌，严重影响患者的身心健康[3,4]。现代研究表明 e 抗原(HBeAg)呈阳性可明显提高 HBV 病毒载量，后者虽对肝细胞无直接损伤，但是可通过免疫应答与炎性反应等损伤肝细胞，导致肝功能障碍[5,6]。HBeAg 阳性患者经抗病毒治疗后出现 HBeAg 阴性继而发生血清学转换，是 HBV 感染获得免疫控制的指标[7]。在慢性乙型肝炎的治疗中，核苷(酸)类似物对 HBV 的复制有显著抑制作用，但在促进 e 抗原血清转换方面效果比较差[8,9]。干扰素有利于促进 e 抗原血清转换，而对 HBV 的复制抑制作用相对较差[10]。其中替诺福韦可通过抑制 HBV DNA 链延长，从而阻断病毒复制路径阻断，控制乙型肝炎向肝硬化进展[11,12]。本文具体探讨了替诺福韦联合聚乙二醇干扰素α-2b 注射液对慢性乙型肝炎患者 HBe Ag 血清学转换率和阴转率的影响，以明确联合用药的应用价值。

1 资料与方法

1.1 研究对象

2018 年 2 月到 2020 年 8 月选择在本院联合汀州医院诊治的慢性乙型肝炎患者 104 例，纳入标准：符合慢性乙型肝炎的诊断标准；年龄 18～60 岁；HBeAg 阳性患者；临床资料完整；患者及家属均知情，签订知情承诺书；谷丙转氨酶(ALT)或者谷草转氨酶(AST)高于正常值上限。排除标准：妊娠期、哺乳期女性，有生育需求的女性；对本研究相关药物过敏或存在禁忌者；精神疾病家族史者；合并其他感染性病毒性疾病者；严重感染者；心力衰竭、慢性阻塞性肺病、心力衰竭、视网膜疾病等基础疾病，有自身免疫性、失代偿期、药物性、遗传代谢性、酒精性及肝脏疾病者；患者不能合作或正在参加其他药物试验者。

根据随机数字表法把患者分为联合组与对照组，各 52 例，两组一般资料对比无差异(P>0.05)，见表 1。

表 1 两组一般资料对比

Table 1 Comparison of two general data

Groups	n	BMI(kg/m²)	SPB(mmHg)	DPB(mmHg)	Course (years)	Gender (M/F)	Age (years)
Joint group	52	22.98± 3.22	134.98± 18.44	85.36± 11.23	3.29± 0.28	27/25	48.34± 3.42
Control group	52	22.09± 3.45	132.76± 19.02	85.67± 10.63	3.32± 0.25	26/26	48.43± 3.82

1.2 治疗方法

对照组：给予聚乙二醇干扰素 α-2b 注射液治疗，皮下注射聚乙二醇干扰素 α-2b 注射液(国药准字 S20160001，厦门特宝生物工程股份有限公司)180 μg，1 次 / 周。

联合组：在对照组治疗的基础上给予口服富马酸替诺福韦二吡呋酯片（Aspen Port Elizabeth (Pty)Ltd.，注册证号 H20130589，规格：0.3 g/ 片）0.3 g，1 次 /d。

两组都治疗观察 48 w。

1.3 观察指标

(1) 在治疗前后检测患者的 HBeAg 血清学转换情况及 H-DNA 的转阴情况。其中 HBV DNA 转阴指检测不到或低于检测下限 (<500 拷贝 /mL)，HBeAg 血清学转换指 HBeAg 转阴且抗 -HBe 转阳。(2)在治疗前后抽取患者的静脉血 2 mL，离心取上清，采用全自动生化仪检测血清谷丙转氨酶(ALT)、谷草转氨酶(AST)含量。试剂盒及检测仪器由德国罗氏公司提供。

1.4 统计学处理

采用 SPSS Statistics 21.00，计量数据以均数± 标准差表示(对比为 t 检验)，计数数据以百分比表示(对比为卡方 x^2 检验)，检验水准为α=0.05。

2 结果

2.1 HBe Ag 血清学转换率对比

治疗后联合组的 HBe Ag 血清学转换率为 11.54 %(6/52)，高于对照组的 3.85 %(2/52)，但是对比无统计学意义(x^2=2.167，P=0.269；P>0.05)，见表 2。

表 2 两组 HBe Ag 血清学转换率对比(例，%)

Table 2 Comparison of HBe Ag seroconversion rate between the two groups (n, %)

Groups	n	HBe Ag serological conversion	HBe Ag serological conversion rate
Joint group	52	6	11.54%
Control group	52	2	3.85%

2.2 HBV DNA 转阴率对比

治疗后联合组的 HBV DNA 转阴率为 100 %(52/52)，高于对照组的 71.17 %(37/52)，经过对比差异有统计学意义(x^2=17.528，P<0.001；P<0.05)，见表 3。

2.3 血清 ALT 与 AST 变化对比

治疗前，两组的血清 ALT 与 AST 值对比无统计学意义(P>0.05)，两组治疗后的血清 ALT 与 AST 值低于治疗前，且联合组低于对照组，经过对比差异有统计学意义(P<0.05)，见表 4。

3 讨论

慢性乙型肝炎是当前全世界都面临着较为严峻的公共卫生问题，早期患者多表现为恶心、肝部不适、呕吐、乏力等症状，

后续可发展为肝硬化、肝癌等[13,14]。慢性乙型肝炎的发病机制还不明确，HBeAg 阳性慢性乙型肝炎病理机制相对复杂，临床普遍认为其病情进展的关键因素在于 HBV-DNA 持续复制与 HBeAg 阳性持续存在[15]。因此该病在临床上的治疗关键环节在于抗病毒治疗，以期抑制乙肝病毒复制活动，达到 HBV-DNA 以及 HBeAg 转阴，从而达到控制、延缓病情进展的目的[16,17]。

表 3 两组 HBV DNA 转阴率对比(例，%)

Table 3 Comparison of HBV DNA conversion rate between the two groups (n,%)

Groups	n	HBV DNA to negative	HBV DNA to negative rate
Joint group	52	52	100%*
Control group	52	37	71.15%

Note: compare with the control group, *P<0.05.

表 4 两组治疗前后血清 ALT 与 AST 变化对比(U/L，$\bar{x}\pm s$)

Table 4 Comparison of changes in serum ALT and AST between the two groups before and after treatment (U/L, $\bar{x}\pm s$)

Groups	n	ALT		AST	
		Pretherapy	Post-treatment	Pretherapy	Post-treatment
Joint group	52	176.20± 12.47	41.48± 3.48#*	167.65± 21.47	38.76± 7.22#*
Control group	52	178.87± 13.22	56.73± 4.14#	168.09± 18.29	53.87± 8.11#

Note: compare with the pretherapy, #P<0.05; compare with the control group, *P<0.05.

当前慢性乙型肝炎的治疗方法比较多，包括保肝抗炎、抗病毒、抗纤维化、增强免疫等[18]。其中聚乙二醇干扰素α-2b 注射液为干扰素类药物，主要是由干扰素 α-2b 结合大分子聚乙二醇而制成，可维持较长药物有效浓度时间，从而显著延长半衰期[19,20]。该药具有显著抗病毒作用，可加快激活相关基因转录，也可通过与细胞表面特异性受体结合，从而抑制病毒 DNA 复制 [21]。本研究显示治疗后联合组的 HBe Ag 血清学转换率为 11.54 %，高于对照组的 3.85 %；治疗后联合组的 HBV DNA 转阴率为 100 %，高于对照组的 71.17 %，表明替诺福韦联合聚乙二醇干扰素 α-2b 注射液治疗慢性乙型肝炎能提高患者的 HBe Ag 血清学转换率和阴转率。从机制上分析，替诺福韦作为腺嘌呤核苷类似物，可降低 HBV 逆转录酶活性，终止 DNA 链延长，从而可抑制 HBV 复制[22]。特别是其与干扰素的联合使用可以发挥优势互补，可发挥更强的抗病毒活性[23]。本研究与陈若雷[24]的研究类似，该学者观察替诺福韦酯联合拉米夫定抗病毒治疗对耐药慢性乙肝患者 HBV DNA 转阴率及 HBeAg 阳性血清学转换率的影响，结果显示治疗后究组血清 HBV DNA 转阴率为 85.71 %，显著高于对照组 69.64 %，治疗后研究组 HBeAg 阳性血清学转换率为 25.00 %，显著高于对照组 10.71 %。但是临床对于替诺福韦联合聚乙二醇干扰素 α-2b 注射液治疗慢性乙型肝炎的应用极少，后续研究需要深入探究联合应用的优势。

慢性乙型肝炎的治疗原则为最大限度地长期抑制 HBV 复制，减轻肝细胞炎症坏死及肝脏纤维组织增生，延缓和减少肝功能衰竭、肝硬化失代偿、肝细胞癌和其他并发症的发生，改善患者生命质量，延长其生存时间。对于部分适合条件的患者，应追求临床治愈。不过治疗疗效受多种因素影响，包括 HBV 的生物学特点、患者自身免疫能力、抗病毒药物的使用等[25]。干扰素为慢性乙型肝炎最为主要的抗病毒药物之一，替诺福韦也是临床一线推荐的慢性乙型肝炎治疗药物[26]。本研究显示两组治疗后的血清 ALT 与 AST 值低于治疗前，联合组低于对照组。与林志鹏[27]等学者的研究类似，该学者观察替诺福韦联合聚乙二醇干扰素 α2a 注射液治疗耐药慢性乙型病毒性肝炎患者的临床疗效和安全性，结果显示治疗后实验组的血清 ALT、AST 水平显著低于对照组。与本研究不同的林志鹏等人的实验对照组给予替诺福韦，实验组在对照组的基础上给予聚乙二醇干扰素 α2a 注射液，与本研究刚好形成互补，互相验证，这也是本研究的分组上的不足。从机制上分析，替诺福韦作为一种具有水溶性的核苷酸类逆转录酶抑制剂，经口服进入体内后可迅速产生活性物质替诺福韦，然后转化为替诺福韦双磷酸盐，可直接竞争性结合脱氧核糖底物，发挥抑制 HBV 复制的目的，从而有利于促进改善患者的肝功能[28,29]。

替诺福韦在临床上的使用具有高耐药屏障效果，肝炎患者长期服药耐药率很低，且具有很好的安全性[30]。聚乙二醇干扰素对 HBV 的复制以及病毒蛋白的表达有明显抑制效果，也能发挥抗病毒及免疫调节作用[31,32]。

总之，替诺福韦联合聚乙二醇干扰素 α-2b 注射液对慢性乙型肝炎患者能提高 HBe Ag 血清学转换率和阴转率，改善患者的肝功能和抗肝纤维化作用。本研究也存在一定的不足，样本量少，结果可能也会存在一定程度的偏倚，同时没有进行替诺福韦的单独用药分析，没有进行随访，也没有深入探究联合用药的机制，将在后续研究中联合多家三甲医院，扩大样本量进行分析、探讨。

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