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恩替卡韦联合异甘草酸镁注射液对慢性乙型肝炎患者血清 IL-2、IL-10、IL-17、MIF 及外周血 T 细胞亚群水平的影响 *

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摘要 目的:探讨恩替卡韦联合异甘草酸镁注射液对慢性乙型肝炎患者血清白细胞介素 -2(IL-2)、白细胞介素 -10(IL-10)、白细胞介素 -17(IL-17)、巨噬细胞移动抑制因子(MIF)及外周血 T 细胞亚群水平的影响。**方法:**选择我院 2015 年 6 月 ~2016 年 12 月收治的 92 例慢性乙型肝炎患者,并按不同治疗方式分为对照组与研究组,每组 46 例。对照组采用恩替卡韦治疗,研究组基于对照组加以异甘草酸镁注射液治疗。比较两组的临床疗效,治疗前后血清 IL-2、IL-10、IL-17、MIF、谷丙转氨酶(ALT),谷草转氨酶(AST),总胆红素(TbiL)水平,外周血 $CD3^+$、$CD4^+$、$CD8^+$、$CD4^+/CD8^+$ 的变化及不良反应的发生情况。**结果:**治疗后,研究组总有效率高于对照组[93.47% vs. 71.74%],差异有统计学意义(P<0.05);两组血清 IL-2 水平及外周血 $CD3^+$、$CD4^+$、$CD4^+/CD8^+$ 水平均较治疗前显著上升,且研究组以上指标均明显高于对照组,两组血清 IL-10、IL-17、MIF、ALT、AST、TbiL 水平及外周血 $CD8^+$ 水平均较治疗前显著下降,且研究组以上指标均明显低于对照组,差异均有统计学意义(P<0.05)。两组不良反应发生率比较差异无统计学意义(P>0.05)。**结论:**恩替卡韦联合异甘草酸镁注射液对慢性乙型肝炎患者的效果优于单用恩替卡韦,可能与其显著升高血清 IL-2、外周血 $CD3^+$、$CD4^+$、$CD4^+/CD8^+$ 水平及降低血清 IL-10、IL-17、MIF 和外周血 $CD8^+$ 水平有关。

关键词:慢性乙型肝炎;恩替卡伟;异甘草酸镁注射液;白细胞介素;巨噬细胞移动抑制因子;T 细胞亚群

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Influence of Entecavir Combined with Magnesium Glycyrrhizin Injection on the serum IL-2, IL-10, IL-17, MIF, Levels and Peripheral Blood T Cell Subgroups of patients with Chronic Hepatitis B*

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ABSTRACT Objective: To research the influence of entecavir combined with magnesium glycyrrhizin injection on the serum interleukin-2 (IL-2),interleukin-10 (IL-10) and interleukin-17 (IL-17), macrophage migration inhibitory factor (MIF) levels and peripheral blood T cell subgroups of patients with chronic hepatitis B. **Methods:** 92 cases of patients with chronic hepatitis B admitted from June 2015 to December 2016 were selected and divided into the control group and the research group according to different treatment method. The control group was treated with entecavir, while the research group was treated with magnesium glycyrrhizin injection based on the control group. The clinical curative effect, levels of serum IL-2, IL-10, IL-17, MIF, alanine aminotransferase (ALT), aspertate aminotransferase (AST), total bilirubin (TbiL), peripheral blood $CD3^+$, $CD4^+$, $CD8^+$, $CD4^+/CD8^+$ levels before and after treatment as well as the incidence of adverse reactions were compared between two groups. **Results:** After treatment, the total effective rate of research group was higher than that of the control group [93.47% vs. 71.74%](P<0.05). The levels of serum IL-2, peripheral blood $CD3^+$, $CD4^+$, $CD4^+/CD8^+$ in both groups were significantly higher than those before treatment, which were higher in the research group than those of the control group, the serum levels of IL-10, IL-17, MIF, CD8+, ALT, AST, TbiL of both groups were lower than those before treatment, which were lower in the research group than those of the control group (P<0.05). No significant difference was found in the incidence of adverse reactions between two groups (P>0.05). **Conclusion:** Entecavir combined with magnesium isoglycyrrhizinate injection is more effective than the entecavir alone on the patients with chronic hepatitis B, it may be related to the significant increase of serum IL-2 expression, peripheral blood $CD3^+$, $CD4^+$, $CD4^+/CD8^+$ levels and decrease of serum IL-10, IL-17, MIF levels and peripheral blood $CD8^+$ level.

Key words: Chronic hepatitis b; Entika wai; Magnesium glycyrrhizin injection; Interleukin; Macrophage mobile inhibiting factor; T cell subgroup

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前言

乙型肝炎是指感染乙型肝炎病毒后(HBV)所引发的疾病，可分为急性和慢性，临床研究证实多数成年急性乙型肝炎患者可自愈[1]。慢性乙型肝炎传染率高，可经母婴、血液、性接触、医源性传播，能够引起发热、疲劳等全身表现，肝功能异常、上腹部不适、厌油、食欲低下等消化道表现，黄疸、肝区疼痛、肿胀等表现，且可导致肝原性糖尿病、脂肪肝、肝硬化、高胆红素血症等系列并发症，甚者可出现肝癌，严重危害患者的生活质量[2,3]。国外研究表明 HBV 感染后能够刺激机体发生免疫反应，引起肝脏出现炎症损伤，同时免疫功能紊乱又可促进 HBV 的复制，形成恶性循环。其中，IL-2、IL-10、IL-17 及 MIF 为代表性的免疫影响因子，同时 T 细胞亚群又能参与机体细胞免疫，客观反映机体的免疫状态，积极调整免疫功能可促进疾病恢复[4,5]。

恩替卡韦作为一种抗 HBV 药物，可使 HBV 复制受到明显抑制，延缓疾病的进程，发挥抗病毒作用，且耐药率较低，能够长时间的控制病情。但 Yong YK 等[6]研究显示单用恩替卡韦的疗效欠佳，因此需辅助其他药物治疗。异甘草酸镁作为一种抗炎保肝药物，不仅能够对肝细胞膜发挥保护作用，同时可起到抗过敏、抗炎等效果[7,8]。目前，国内关于二者联合应用的报道较少。本研究旨在分析恩替卡韦联合异甘草酸镁注射液对慢性乙型肝炎患者血清 IL-2、IL-10、IL-17、MIF 及外周血 T 细胞亚群的影响，以期指导临床治疗。

1 资料与方法

1.1 一般资料

选择我院 2015 年 6 月 ~2016 年 12 月收治的 92 例慢性乙型肝炎患者，入选标准：⓪ 符合相关《慢性乙型肝炎防止指南》标准[9]：HbeAg、HBeAg 呈阳性，谷丙转氨酶(ALT)或者谷草转氨酶(AST)高于正常上限值 2 倍；乙型肝炎病程超过半年；全身无其他严重病变。排除标准：自身免疫系统障碍；其他病毒性肝炎、慢性重型乙型病毒性肝炎、肝硬化失代偿期、肝癌；妊娠期或者哺乳期；近 3 个月内使用过核苷类、干扰素类抗 HBV 药物；药物或者酒精滥用史。按不同治疗方式将所有患者分为对照组与研究组，每组 46 例。对照组中，女 19 例，男 27 例；年龄 22~59 岁，平均(35.71± 3.97)岁。研究组中，女 22 例，男 24 例；年龄 21~60 岁，平均(36.22± 4.20)岁。两组基础资料比较差异均无统计学意义，存在可比性(P>0.05)。

1.2 治疗方法

对照组接受恩替卡韦治疗，口服 0.5 mg 的恩替卡韦片(0.5mg/ 片，国药准字 H20100020，150413)，qd，持续治疗 16 周。研究组基于对照组加以异甘草酸镁注射液治疗，静脉滴注 200 mg 异甘草酸镁注射液 (10 mL: 50mg，国药准字 H20051942，140418)，第 1~4 周每天 1 次，5~8 周，间隔 1 天用药，9~16 周每周 2 次用药，持续治疗 16 周。记录期间的不良反应，嘱患者定期回院复诊，于治疗结束时评估疗效。

1.3 观察指标

1.3.1 **临床疗效观察** 临床体征及表现显著缓解或者消失，生化指标未见异常即显效；临床体征及表现有一定减轻，部分生化指标未恢复至正常水平即好转；临床体征、表现及生化指标未见减轻，或者加重即无效[10]。

1.3.2 **指标观察** 于用药前及结束时抽取患者 2 mL 外周静脉血，予以血清分离机将其常规分离，并于低温环境中保存待检。血清 IL-2、IL-10、IL-17、MIF 水平选用酶联免疫法进行，$CD3^+$、$CD4^+$、$CD8^+$ 选用流式细胞术进行，血清 ALT、AST、TbiL 水平选用生化分析仪检测。

1.4 统计学分析

采用 SPPS18.0 进行数据处理，计量资料以($\bar{x}\pm s$)表示，组间比较选用 t 检验，用[(例)%]表示计数资料，组间比较用 x^2 检验，以 P<0.05 为差异具有统计学意义。

2 结果

2.1 两组临床疗效比较

研究组总有效率为 93.47%，显著高于对照组(71.74%，P<0.05)，见表 1。

表 1 两组临床疗效的比较[例(%)]

Table 1 Comparison the clinical curative effect between two groups[n(%)]

Groups	Effective	Improve	Invalid	Total effective rate
Control group(n=46)	20(43.48)	13(28.26)	13(28.26)	33(71.74)
Research group(n=46)	28(60.87)	15(32.61)	3(6.52)	43(93.47)

Note: Compared with the control group, #P<0.05.

2.2 两组治疗前后血清 IL-2、IL-10、IL-17、MIF 水平的比较

治疗前，两组血清 IL-2、IL-10、IL-17、MIF 水平比较差异无统计学意义(P>0.05)；治疗后，两组血清 IL-2 水平均较治疗前显著上升，且研究组明显高于对照组，两组血清 IL-10、IL-17、MIF 水平均较治疗前下降，且研究组以上指标均显著低于对照组(P<0.05)，见表 2。

2.3 两组治疗前后 T 细胞亚群的比较

治疗前，两组 T 细胞亚群比较差异无统计学意义(P>0.05)；治疗后，两组 $CD3^+$、$CD4^+$、$CD4^+/CD8^+$ 均较治疗前显著上升，且研究组明显高于对照组，两组 $CD8^+$ 均较治疗前显著下降，且研究组明显低于对照组(P<0.05)，见表 3。

2.4 两组治疗前后肝功能的比较

治疗前，两组肝功能指标比较差异均无统计学意义(P>0.05)；治疗后，两组血清 ALT、AST、TbiL 水平均较治疗前显著下降，且研究组以上指标下降程度更明显(P<0.05)，见表 4。

2.5 两组不良反应发生情况的比较

用药期间，对照组与研究组血压增高(4 例 vs2 例)、心悸(2 例 vs3 例)的发生率比较差异均无统计学意义(P>0.05)。

表 2 两组治疗前后血清 IL-2、IL-10、IL-17、MIF 水平的比较($\bar{x}\pm s$)

Table 2 Comparison of the serum IL-2, IL-10, IL-17, MIF levels between two groups before and after the treatment ($\bar{x}\pm s$)

Groups	Time	IL-2(ng/L)	IL-10(ng/L)	IL-17(μg/L)	MIF(μg/L)
Control group(n=46)	Before treatment	111.56± 13.86	50.62± 6.24	21.82± 2.61	51.63± 6.37
	After treatment	150.91± 18.92*	28.50± 3.50*	12.40± 1.55*	16.85± 2.11*
Research group(n=46)	Before treatment	112.71± 14.62	51.24± 6.79	22.47± 2.53	51.06± 6.12
	After treatment	186.65± 23.25#*	18.77± 2.26#*	7.91± 0.98#*	10.79± 1.30#*

Note: Compared with the control group, #P<0.05; Compared with before treatment , *P<0.05.

表 3 两组治疗前后 T 细胞亚群比较($\bar{x}\pm s$)

Table 3 Comparison of the T cell subsets between two groups before and after the treatment ($\bar{x}\pm s$)

Groups	Time	$CD3^+$(%)	$CD4^+$(%)	$CD8^+$(%)	$CD4^+/CD8^+$
Control group(n=46)	Before treatment	51.40± 6.37	32.13± 4.12	31.88± 3.97	1.05± 0.13
	After treatment	55.44± 6.80*	35.90± 4.51*	29.17± 3.99*	1.24± 0.16*
Research group(n=46)	Before treatment	50.97± 6.99	32.78± 4.59	31.45± 3.61	1.09± 0.15
	After treatment	59.76± 7.32#*	39.81± 4.88#*	26.09± 3.20#*	1.50± 0.19#*

Note: Compared with the control group, #P<0.05; Compared with before treatment , *P<0.05.

表 4 两组治疗前后肝功能的比较($\bar{x}\pm s$)

Table 3 Comparison of liver function between two groups before and after the treatment ($\bar{x}\pm s$)

Group	Time	ALT(U/L)	AST(U/L)	TbiL(μmol/L)
Control group(n=46)	Before treatment	409.60± 51.24	329.06± 41.23	75.60± 9.37
	After treatment	181.34± 22.62*	153.12± 19.12*	45.62± 5.60*
Research group(n=46)	Before treatment	408.64± 51.90	327.65± 40.86	76.11± 9.12
	After treatment	110.77± 13.72#*	102.49± 12.75#*	25.70± 3.12#*

Note: Compared with the control group, #P<0.05; Compared with before treatment , *P<0.05.

3 讨论

慢性乙型肝炎为肝脏常见疾病,其病程迁延,传染性强,临床治疗难度相对较大，抗病毒治疗是其重要手段，旨在抑制 HBV 复制,改善肝脏纤维化、坏死及炎症,提高肝功能,防止并发症的发生[11]。恩替卡韦是一类核苷酸类似物,为抵抗乙型肝炎病毒的首选药物,经口服后能够于短时间内吸收,并于各组织内分布,但人体实验结果显示其血浆蛋白结合率较低,半衰期较短[12]。恩替卡韦可起到强效的抗 HBV 病毒复制作用,可于体内经磷酸化为活性较强的三磷酸盐，和 HBV 三磷酸的脱氢鸟嘌呤核苷相互反应,抑制 HBV 的多聚酶,进而阻止 HBV 的延伸,最终阻断其复制,起到治疗慢性乙型肝炎的效果[13,14]。动物实验表明恩替卡韦无相关耐药性,但其停药反应明显,可能加重病情,有一定局限性[15]。

异甘草酸镁注射液属肝细胞保护剂,是一种来自于甘草中的提取物,经注射后能够于短时间内分布,且半衰期相对较长,能够促进氧自由基的清除,缓解炎症反应,利于肝细胞恢复及再生[16]。药效研究显示急性肝损伤大鼠应用异甘草酸镁注射液后能够避免转氨酶上升,抑制炎症细胞发生浸润,缓解肝细胞坏死及变性，同时能够改善肝组织的纤维化及炎症活动度,并对免疫性肝损伤有良好的保护作用，使肝组织受损降低[17,18]。Soriano V 等[19]研究表明异甘草酸镁注射液联合其他保肝药物或者单用均具有较好的安全性及效果。本研究结果显示恩替卡韦联合异甘草酸镁注射液组总有效率显著高于单用恩替卡韦组,证实其临床效果肯定,可能与二者作用机制不同可起到协同作用,从而提高疗效有关[20,21]。

临床研究证实机体感染 HBV 后能够引发系列的免疫反应,进而造成免疫调节功能出现紊乱,机体感染抗病毒细胞的免疫能力是决定慢性乙型肝炎转归的重要因素 [22,23]。Th1/Th2 免疫平衡是机体免疫功能正常的关键,Th1 细胞能够调控细胞免疫,提高细胞毒性 T 细胞功能,增强机体抵抗感染作用,促进病毒的清除[24]。Th2 细胞能够使 Th1 细胞产生抑制,引起体液免疫增加,导致组织受损。IL-2 来自于 Th1 细胞,为调控免疫应答的重要因子,能够利于 T 细胞的生长,诱导分化 NK 细胞,确保机体的免疫功能正常,也可参与抗体反应、造血和肿瘤监视[25]。IL-10 是具有多向性生物学活性的强免疫抑制因子,由 Th2 细胞所生成,可介导 Th1 和 Th2 两类细胞之间的相互调节,使 Th1 细胞的增殖受到影响,抑制免疫应答反应,导致机体清除 HBV 能力下降[26]。IL-17 存在相对较强的促炎作用,可诱导基质金属蛋白酶及其他促炎介质的分泌，促进中性粒细胞、T 细胞及树状细胞转移至炎症部位，加剧机体炎症反应，并可导致 Th2/Th2 细胞失衡,增加 Th2 细胞的分泌,抑制 Th1 细胞表达,诱导系列变态反应性病变[27]。MIF 属内分泌免疫物质,也是前炎性因子,能够刺激其他炎症因子的释放。

外周血 T 细胞亚群能够客观的反映机体的免疫功能状态。T 细胞免疫反应主要参与 HBV 清除、肝组织损伤反应，通过检测此类指标水平对于慢性乙型肝炎的转归有着重要价值[28]。$CD3^+$ 仅存在于 T 细胞表面，能够参与 T 细胞的信号转导，其水平能够客观反映外周血成熟 T 细胞的状态。$CD4^+$ 是人体免疫系统中的一种重要免疫细胞，其主要表达于 Th 细胞，是 Th 细胞 TCR 识别抗原的供受体，能够抑制病毒的复制及变异，减少体内的病毒载量，避免免疫损伤的进一步发展。$CD8^+$ 是一种细胞毒性亚群，能够造成细胞的功能紊乱，机体正常状态下 $CD4^+/CD8^+$ 的比值相对稳定，维持机体的正常免疫功能[29,30]。本研究结果显示两组治疗后血清 IL-2、外周血 $CD3^+$、$CD4^+$、$CD4^+/CD8^+$ 水平均较治疗前显著上升，血清 IL-10、IL-17、MIF 水平及外周血 $CD8^+$ 明显下降，但恩替卡韦联合异甘草酸镁注射液组改善更为明显，可能其更能有效抑制 HBV 复制，从而调节机体免疫反应，为疾病恢复创造良好基础。且本研究显示，联合治疗者肝功能改善更为明显，但两组均有少数不良反应发生，但表现较轻，未引起严重后果。

综上所述，恩替卡韦联合异甘草酸镁注射液对慢性乙型肝炎患者的效果优于单用恩替卡韦，可能与其显著升高血清 IL-2、外周血 $CD3^+$、$CD4^+$、$CD4^+/CD8^+$ 水平及降低血清 IL-10、IL-17、MIF 和外周血 CD8+ 水平有关。

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