双环醇片治疗慢性肝炎高转氨酶血症的疗效观察

虞 胜 祝峻峰 李 勇

(上海中医药大学附属市中医医院 消化科 上海 200071)

摘要 目的:观察双环醇片治疗慢性肝炎高转氨酶血症的临床疗效。方法:选择住院或门诊慢性肝炎高转氨酶血症患者 280 例,随机分为治疗组和对照组,治疗组 141 例,对照组 139 例。治疗组在常规保肝治疗的基础上加用双环醇片 25m 每日 3 次口服,对照组在常规保肝治疗的基础上加用甘利欣胶囊 150mg 每日 3 次口服。疗程均为 4 周。治疗前后每周详细记录患者症状、体征、肝功能、肾功能、电解质、及血尿常规,同时记录治疗过程中的不良反应及停药后随访 3 个月。结果:两组均有显著疗效,肝功能生化指标与治疗前相比有显著性差异(治疗组 P<0.01,对照组 P<0.05),治疗组明显优于对照组(P<0.05),且治疗组出现的不良反应明显少于对照组。结论:双环醇片治疗慢性肝炎高转氨酶血症疗效好,不良反应较少,值得临床推广。

关键词:双环醇片;高转氨酶血症;疗效观察

中图分类号:R512.62 **文献标识码**:A **文章编号**:1673-6273(2011)12-2298-03

Observation on the effects of Bicyclol on high aminotransferase of chronin hepatitis

YU Sheng, ZHU Jun-feng, LI Yong

(Shanghai Municipal Hospital of Traditional Chinese Medicine affiliated to Shanghai TCM University, Shanghai 200071)

ABSTRACT Objective: To observe the clinical effect of Bicyclol on high aminotransferase of chronic hepatitis. Methods: In-patient or out-patient hospital chronic hepatitis patients with hyperlipidemia high aminotransferase 280 cases were randomly divided into treatment and control groups, the treatment group 141 cases, 139 cases of the control group. In the conventional treatment group on the basis of protective and treatment plus a daily Bicyclol 25mg tid po; the control group in the conventional treatment of liver protection on the basis of protective and treatment plus a daily glycyrrhizinate capsules 150mg tid po. Courses are four weeks. Detailed records of a week before and after treatment in patients with symptoms and signs, liver function, kidney function, electrolytes, and hematuria conventional, and treatment records in the process of adverse reactions and follow-up after stopping three months. Results: The two groups were significantly effect, biochemical indicators of liver function before treatment compared with a significant difference (treatment group P <0.01, control group P <0.05), the treatment group was significantly better than the control group (P <0.05), the treatment group and the adverse reaction was less than the control group. Conclusion: All kinds of chronic hepatitis high aminotransferase treated with the bicyclol not only has the safety, affirmative advantage in curative effect, but fewer adverse reactions, deserve the clinical expansion.

Key words: Bicyclol; High aminotransferase; Observation

Chinese Library Classification: R512.62 Document code: A

Article ID:1673-6273(2011)12-2298-03

前言

双环醇片是我国第一个具有国际自主知识产权的创新药物,为验证其治疗各种慢性肝炎高转氨酶血症患者的临床疗效,特进行了如下临床观察。

1 资料与方法

1.1 一般资料

我们选择自 2009 年 6 月 -2010 年 12 月在我科住院或门诊治疗的各种慢性肝炎高转氨酶血症患者 280 例。其中男性 156 例,女性 124 例,年龄最小 18 岁,最大 68 岁,平均 45.7±11.2 岁。其中:乙型肝炎 102 例;酒精性脂肪性肝炎 54 例;非酒精性脂肪性肝炎 35 例;药物性肝炎 29 例;丙型肝炎 14 例;其它 46 例。随机分为两组,治疗组 141 例,对照组 139 例。两组患者在临床表现、病情程度、性别、年龄、病因、病程等方面,两组差异无统计学意义(P>0.05),具有可比性。

1.2 治疗方法

治疗组每日在常规保肝治疗的基础上加用双环醇片 25mg(规格:25mg/ 片,北京协和药厂,批准文号:国药准字 H20040467),每日 3 次口服;对照组在常规保肝治疗的基础上加用甘利欣胶囊 150mg(规格:50mg/ 粒,江苏正大天晴药业股份有限公司,批准文号:国药准字 H10940191),每日 3 次口服。同时针对病因进行相关综合治疗,疗程均为 4 周。治疗前后每周详细记录患者症状、体征、肝功能、肾功能、电解质、及血尿常规,同时记录治疗过程中的不良反应及停药后随访 3 个月。

1.3 临床疗效评价方法

作者简介:虞胜(1976-),女,硕士研究生,主治医师,研究方向:肝脏疾病的中西医结合治疗,电话:02156639828*2302;

E-mail:0139@stcmh.stnc.com.cn

(收稿日期:2011-02-06 接受日期:2011-02-28)

根据自觉症状、肝功能改善情况综合评价。疗效评定：1）显效：疗程结束时患者临床症状基本消失，转氨酶恢复正常；2）有效：疗程结束时患者临床症状基本消失，转氨酶较前下降 50%以上；3）无效：疗程结束时患者临床症状无改善或改善不明显，转氨酶较前下降 50%以下。显效和有效合计称为有效，据此计算总有效率。

表 1 两组治疗前后生化指标变化情况

Table1 Before and after treatment biochemical changes in two groups

		0W	1W	2W	3W	4W	6W	8W	12W	16W
治疗组 Treatment group	TBIL	21.8± 6.42	19.4± 6.45	18.7± 6.4	17.9± 6.9	18± 6.3	18.2± 5.2	19± 5.1	18.6± 6.5	16.9± 5.3
	ALT	334± 86.3	172± 46.5	93± 29.1	46± 16.7	31± 12.5	30± 14.1	29± 13.5	25± 12.1	23± 10.9
	AST	287± 78.7	161± 47.1	88± 30.5	36± 20.3	30± 11.9	28± 15.2	27± 16.2	26± 15.9	22± 9.8
	Bun	5.0± 1.6	5.0± 2.0	5.1± 1.8	5.1± 1.9	5.2± 1.5	5.1± 2.1	5.1± 1.9	5.0± 1.4	5.0± 1.3
	Cr	78± 36.5	77± 38.6	79± 35.4	81± 32.6	76± 30.8	73± 40.2	72± 41.6	75± 35.5	76± 36.7
	K	4.6± 0.6	4.1± 0.5	4.0± 0.6	3.9± 0.5	4.0± 0.6	4.2± 0.7	4.3± 0.6	4.4± 0.5	4.5± 0.7
	Na	140± 5.2	140± 5.4	140± 4.8	141± 4.9	141± 4.7	140± 5.1	140± 5.2	140± 4.8	140± 5.0
	Cl	102± 7.8	102± 7.5	101± 8.0	102± 7.5	102± 6.9	102± 7.9	101± 9.0	102± 8.5	102± 7.6
对照组 Control group	TBIL	19.7± 6.5	18.9± 6.4	18.8± 6.3	17.8± 5.9	18.4± 6.3	18.1± 5.3	19.2± 4.8	18.5± 6.5	16.8± 4.9
	ALT	328± 88.5	216± 51.8	155± 34.1	101± 25.7	75± 20.7	79± 24.3	81± 20.5	85± 29.8	82± 32.9
	AST	279± 81.3	198± 65.4	152± 54.2	98± 35.6	70± 21.9	75± 19.2	79± 21.2	80± 35.6	81± 37.8
	Bun	4.9± 2.1	5.0± 1.8	5.1± 1.2	5.1± 1.8	5.2± 1.0	5.1± 1.9	5.0± 1.6	5.0± 1.7	5.0± 2.0
	Cr	68± 46.5	70± 39.5	75± 32.5	80± 32.6	75± 29.8	74± 40.5	70± 40.6	67± 39.5	69± 35.7
	K	4.5± 0.7	4.0± 0.5	4.0± 0.6	3.8± 0.6	3.7± 0.8	4.1± 0.7	4.2± 0.5	4.3± 0.8	4.5± 0.9
	Na	140± 5.4	141± 4.9	141± 5.2	142± 5.0	142± 5.1	141± 5.6	141± 5.0	140± 5.8	139± 5.2
	Cl	103± 6.5	103± 8.0	104± 5.8	104± 6.5	104± 7.2	104± 5.2	103± 8.0	103± 7.1	103± 6.5

表 2 两组治疗有效性情况

Table2 Effectiveness of two treatment conditions in two groups

	治疗组（Treatment group）								对照组(Control group)							
	TBIL	ALT	AST	Bun	Cr	K	Na	Cl	TBIL	ALT	AST	Bun	Cr	K	Na	Cl
例数(Number)	141	141	141	141	141	141	141	141	139	139	139	139	139	139	139	139
显效(Excellent)	0	79	71	0	0	0	0	0	0	67	61	0	0	0	0	0
有效(Effective)	0	56	61	0	0	0	0	0	0	49	53	0	0	0	0	0
无效(Invalid)	141	6	9	141	141	141	141	141	139	21	25	139	139	139	139	139
有效率 (Effective rate)	0	95.7%	93.6%	0	0	0	0	0	0	83.4%	82.0%	0	0	0	0	0

1.4 统计学处理

计量资料均采用 x± s 表示，两组之间的差别进行 t 检验；等级资料的比较进行秩和检验。

2 结果

2.1 临床疗效分析

治疗组有效率 95.7%，对照组有效率 83.4%。从表 1 可见，治疗组丙氨酸氨基转移酶(ALT)、天冬氨酸氨基转移酶(AST)治疗前与治疗后相比差异有统计学意义($P<0.01$)，对照组丙氨酸氨基转移酶(ALT)、天冬氨酸氨基转移酶(AST)治疗前与治疗后相比差异也有统计学意义($P<0.05$)。而两组间的疗效差异也有统计学意义($P<0.05$)，治疗组明显优于对照组。另治疗组起效时间明显短于对照组，且疗效更巩固，停药后转氨酶反弹率较对照组明显降低，且有统计学意义（$P<0.05$）。

2.2 不良反应

治疗组有 1 例出现头晕，3 例出现皮疹悸，未出现电解质改变；对照组中有 4 例出现头晕，7 例出现心悸，9 例出现血压轻度升高，4 例出现血钾降低，但经一般对症处理后均能缓解，不影响治疗疗程。两组均未引起的水钠潴留等不良反应，变态反应亦未发现。

3 讨论

双环醇片化学名为 4,4′ - 二甲氧基 -5,6,5′ ,6′ - 双(亚甲二氧基)-2- 羟甲基 -2-′ 甲氧羰基联苯，是在五味子素的基础上

人工合成的国家一类新药，具有明显的肝细胞保护作用和一定的抗肝炎病毒作用[1]。临床前研究显示双环醇在多种动物实验性肝损伤模型上能改善肝细胞的损伤，使血清转氨酶明显降低[2-5]。而近年来多项基础研究表明双环醇具有明显抗炎减轻免疫等作用。Yu 等[6]研究发现，双环醇可抑制肝脏丙二醛(MDA)生成的增加和 GSH 的降低，一定程度提高肝细胞抗氧化酶，显著改善由顺铂引起的小鼠肝细胞空泡变性和门脉区炎症细胞的聚集等病理损伤，降低血清中升高的氨基转移酶；Zhao 等[7]研究结果表明，双环醇对酒精引起肝损伤的保护机制主要是在蛋白和基因水平上抑制氧化应激和细胞因子的过表达，同时降低血浆内毒素水平和 CD14 的表达，抑制库普弗细胞活性，从而显著保护急性酒精性肝损伤。Pan 等[8]研究结果提示，双环醇对血清和肝脏脂质代谢的作用与双环醇抗炎、抗脂质过氧化、抑制 Fas/FasL mRNA 的表达和减少肿瘤坏死因子 -α 分泌有关。Bao 等[9,10]在研究中发现，双环醇是 HSPs 的诱导物。双环醇可显著缓解 ConA 诱导的小鼠肝损伤，使小鼠体内的 mRNA 和肝脏 HSPs(HSP27 和 HSP70)蛋白含量增加，抑制 ConA 引起的 κ B 抑制剂的降解和 NF-κB 活化，从而抑制转录因子 NF-κB 介导的肝组织细胞凋亡和坏死。多项临床研究表明双环醇片对非酒精性脂肪肝[11]、药物性肝损伤[12,13]、病毒性肝病[14]均有明确疗效。而高若飞[15]进行双环醇治疗婴儿肝炎的疗效观察，结果表明双环醇治疗婴儿肝炎疗效肯定且停药后不易反弹，同时充分表明双环醇的安全性。根据国内外文献的汇集分析(Meta-analysis)，应用 α - 干扰素治疗后 HBeAg 和 HBV-DNA 转阴率分别为 37%和 33%，安慰剂组分别为 12%和 17%[16-18]，由于双环醇的抗病毒作用有限，对病毒滴度相对较高者 HBV-DNA 转阴的机会较少[19,20]。由此可见，双环醇可实现抗肝细胞坏死、调控凋亡、促进肝细胞再生等作用，从不同角度保护肝细胞，抗炎症损伤。

从上述治疗组和对照组的疗效观察中可见，无论是临床症状的改善，还是生化指标的好转，两组对于慢性肝炎高转氨酶血症患者均具有良好的疗效，两者之间治疗前后均有统计学意义，这也证明了在减轻肝细胞炎症、促进肝细胞功能恢复方面，双环醇片和甘利欣胶囊都是有效的，都是一良好的肝细胞保护剂。但在疗效方面治疗组明显优于对照组。且治疗组起效时间明显短于对照组，疗效更巩固，停药后转氨酶反弹率也较对照组明显降低，同时治疗组出现的不良反应明显少于对照组。结论双环醇片治疗各种慢性肝炎高转氨酶血症不仅疗效好，而且不良反应少，疗效更巩固持久，值得临床推广。

参考文献 (References)

[1] Zhang J Y. New drugs derived from medicinal plants [J].Therapie, 2002,57(2):137-15

[2] 刘耕陶. 双环醇抗病毒与肝保护作用及其作用机制[J].中国新药杂志,2001,10(5):325-327
Liu Geng-tao.The antivirus and hepatoprotective effect of bicyclol and its mechanism of action [J].Chin New Drugs J ,2001,10 (5): 325-327

[3] LIU GT,ZHENG CZ, LI Y,et al. Clinical and Pharmacological study of Bicyclola potential anti-chronic viral hepatitis drug [J].Clin Med Sci J,1999,14 Suppl:51-53

[4] 李烨,戴国炜,李燕. 双环醇对乙酰氨基酚引起小鼠肝脏能量代谢和线粒体功能障碍的影响[J].药学学报,2001,36(10):723-726
Li Ye, Dai Guo-wei, Li Yan, et al. Effect of bicyclol on acetaminopheninduced hepatotoxicity:energetic metabolism and mitochondrial injury in acetaminophen2intoxicated mice [J].Acta Pharm Sin,2001,36(10):723-726

[5] 赵冬梅,刘耕陶.双环醇对刀豆蛋白所致小鼠肝细胞核 DNA 损伤的保护作用[J].中华医学杂志,2001,81(14):844-848
Zhao Dong-mei, Liu Geng-tao. Protective effect of bicyclol on concanaralinAinduced live nuclear DNA injury in mice[J].Natl Med J China, 2001,81(14):844-848

[6] Yu YN, ChenH, LiY. Effect of bicyclol on cisplatin-Induced hepatotoxicity in the hepatocarcinoma 22 tumour-bearing mice [J]. Basic Clin Pharmacol Toxicol, 2009, 104(4): 300-305

[7] Zhao J, ChenH, LiY. Protective effect of bicyclol on acute alcohol-induced liver injury in mice [J]. Eur J Pharmacol, 2008, 586 (1-3):322-331

[8] Pan SY, Dong H, Yu ZL, et al. Bicyclol, a synthetic dibenzocyclooctadiene derivative, decreases hepatic lipids but increases serum triglyceride level in normal and hypercholesterolaemic mice [J]. J Pharm Pharmacol, 2007, 59(12): 1657-1662

[9] Bao XQ, Liu GT. Bicyclol: a novel antihepatitis drug with hepatic heat shock protein 27/70-inducing activity and cytoprotective effects in mice [J]. Cell Stress Chaperones, 2008, 13(3): 347-355

[10] BaoXQ, Liu GT. Induction of overexpression of the 27-and 70-kDa heat shock proteins by bicyclol attenuates concanavalin a-induced liver injury through suppression of nuclear factor-κB in mice [J]. Mol Pharmacol, 2009, 75(5): 1180-1188

[11] 吴杭源,尤德宏.二甲双胍联合双环醇治疗非乙醇性脂肪肝 55 例疗效观察[J].吉林医学,2011,1(32):57-59
Wu Hang-yuan, You De-hong,. The efficacy of metformin combined with bicyclol in the treatment of nonalcoholic steatohepatitis [J]. Jilin Medical Journal, 2011,1(32):57-59

[12] 张凌云.不同剂量双环醇预防妇科肿瘤化疗药物性肝损害研究[J].首都医药,2010,10(17):48-49.
Zhang Ling-yun. The research of different dose bicyclol in prevent gynecological cancer chemotherapeutic drugs induced liver injury[J]. Capital Medicine,2010,10(17):48-49

[13] 巨煜华,李玉芬,吴晓宁.双环醇片联合甘草酸二胺治疗抗结核药物导致肝功能中度损伤的临床研究[J].临床肝胆病杂志,2009,6(25): 448-449
Ju Yu-hua, Li Yue-fen, Wu Xiao-ning. Bicyclol diamine glycyrrhizin treatment of joint anti-TB drugs cause liver damage in clinical studies with moderate[J]. Chinese Journal of Clinical Hepatology,2009,6(25): 448-449

[14] 杨永红,曹公银,丁慧珍等.双环醇片治疗 HBeAg 阳性和阴性慢性乙型肝炎的疗效比较[J].现代中西医结合杂志,2008,19:2979.
Yang Yong-hong, Cao Gong-yin, Ding Hui-zhen, etc. Bicyclol treatment of HBeAg positive and negative chronic hepatitis B compared [J]. Modern Journal of Integrated Traditional Chinese and Western Medicine,2008,19:2979

[15] 高若飞,于静,周喜红.双环醇治疗婴儿肝炎 52 例疗效观察[J].中国医药指南,2010,8(8):93-94
Gao Ruo-fei, Yu Jing, Zhou Xi-hong. Bicyclol treatment of infantile hepatitis 52 cases[J]. Guide of China Medicine,2010,8(8):93-94

(下转第 2327 页)

增强对胶原的敏感性，加快血小板粘附聚集，影响动脉粥样硬化的发生、发展及血栓形成过程。

综上所述，GPⅢaPLA 青岛地区汉族人中突变率极低，其多态位点可能不是阿司匹林抵抗的危险因素。而 GPⅠa807T 等位基因与阿司匹林抵抗显著相关，可能是阿司匹林抵抗的遗传易感因素。但由于病例数较少，各研究入选标准不同，因此本文得出的结论还需要进行更大规模的前瞻性、基因学和流行病学的研究来证实。

参 考 文 献(References)

[1] Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study [J]. Lancet, 2001, 358: 527-33

[2] T. S. Poulsen, B. Jorgensen, L. Korsholm, P. B. Licht, T. Haghfelt, and H. Mickley, "Prevalence of aspirin resistance in patients with an evolving acute myocardial infarction [J]. Thrombosis Research, 2007, 119 (5): 555-562

[3] 陈可冀，薛梅，殷惠军. 血小板活化与冠状动脉粥样硬化性心脏病和血瘀证的关系 [J]. 首都医科大学学报. 2008, 29(3): 266-269
Chen Ke-ji, Xue Mei, Yin Hui-jun. The Relationship between Platelet Activation and Coronary Heart Disease and Blood-stasis Syndrome [J]. Journal of Capital Medical University. 2008, 29(3): 266-269.

[4] Gum PA, Kottke-Marchant K, Welsh PA, White J, Topol EJ. A prospective, blinded determination of the natural history of aspirin resistance among stable patients with cardiovascular disease [J]. J Am Coll ardiol 2003, 41(6):961-5

[5] Mckee SA, Sane DC, Deliargyris EN. Aspirin resistance in cardiovascular disease: A review of prevalence, mechanisms, and clinical significance [J]. Thromb Haemost, 2002, 88(5): 711

[6] Weiss EJ, Bray PF, Tayback M, et al. A polymorphism of a Platelet glycoprotein receptor as an inherited risk factor for coronary thrombosis [J]. N Eng J Med, 1996, 334: 1090

[7] Undas A, Sanak M, Musial J, et al Platelet glycoprotein Ⅲa polymorphism, aspirin, and thrombin generation [J]. Lancet, 1999, 353: 982-983

[8] Szczeklik A, Undas A, Sanak M, et al. Relationship between bleeding time, aspirin, and PLA1/A2 polymorphism of platelet glycoprotein Ⅲa [J]. Br J Haematol, 2000, 110: 965-967

[9] Michelson AD, Furman MI, Goldschmidt, Clermont P, et a1. Platelet GPⅢa PI(A)polymorphisms display different sensitivities to agonists [J]. Circulation, 2000, 101(9): 1013-1018

[10] Cooke GE, Bray PF, Hamlington JD, et al. PLA2 polymorphism and efficacy of aspirin[J]. Lancet, 1998, 351: 1253

[11] Macchi L, Christiaens L, Brabant S, et al. Resistance in vitro to low-dose aspirin is associated with Platelet PLA1 (GPⅢa) polymorphism but not with C807T (GPⅠa/Ⅱa) and C-5T Kozak (GPⅠba) polymorphisms [J]. Am Coll Cardiol, 2003, 42:1115-1119

[12] Pamukcu B, Oflaz H, Nisanci Y. The role of PLAtelet glycoprotein I-IIa polymorphism in the high prevalence of in vitro aspirin resistance in patients with intracoronary stent restenosis [J]. Am Heart, 2005, 149:675-680

[13] 丁枭伟, 杨新春, 王乐丰, 等. 汉族冠心病人 GPⅢa PLA 多态性的初步研究 [J].中国医药导刊, 2006, 8(3): 214-216
Ding Xiao-wei, Yang Xin-chun, Wang Le-feng, et a1. Glycoprotein ma PLA Polymorphism in Pailents With Coronary Artery Disease in Chinese [J]. Chinese Journal of Medicinal Guide, 2006, 8(3): 214-216

[14] 薛梅, 陈可冀, 殷惠军. 汉族人血小板膜糖蛋白Ⅲa PLA 基因多态性与冠心病血瘀证的相关性 [J]. 中西医结合学报, 2009, 7(4): 325-329.
Xue Mei, Chen Ke-ji, Yin Hui-jun. Relationship between polymorphism of platelet membrane glycoprotein Ⅲa and coronary heart disease with blood-stasis syndrome in Chinese Han population [J]. Journal of Chinese Integrative Medicine, 2009, 7(4): 325-329

[15] Kunicki TJ, Kritzik M, et al. hereditary variation in Platelet integrin alpha 2 beta 1 density is associated with two silent polymorphisms in the alpha 2 gene coding sequence [J]. Blood, 1997, 89: 1939-1943

[16] Ajzenberg N, Berroeta C, Philip I, et al. Association of the -92C/G and 807C/T Polymorphisms of the α 2 Subunit Gene With Human Platelets α 2β 1 [J]. Arterioscler Thromb Vasc Biol, 2005, 25: 1756-1760

[17] Moshfegh K, Wuillem in WA, Redondo M, et al. Association of two silent polymorphisms of Platelet glycoprotein PⅠa/Ⅱa receptor with risk of myocardial infarction: a case-control study [J]. Lancet, 1999,353: 351-354

[18] He L, Pappan LK, Grenache DG, et al. The contributions of the alpha 2 beta 1 integrin to vascular thrombosis in vivo [J]. Blood, 2003, 102: 3652-3657

[19] Nikolopoulos GK, Tsantes AE, Bagos PG, et a1. Integrin, Alpha 2 GENe C8O7T Polymorphism and Risk of Ischemic Stroke: a Meta-analysis [J]. Thromb Res, 2007, 119(4):501-510

[20] Angiolillo DJ, Fernandez Ortiz A, Bernardo E, et al. Variability in Platelet aggregation following sustained aspirin and clopidogrel treatment in patients with coronary heart disease and influence of the 807 c/t polymorphism of the glycoprotein ia gene [J]. The American Journal of Cardiology, 2005, 96(8): 1095-1099

(上接第 2300 页)

[16] WON G DKH,CHENG AM, O'ROURKE K,et al. Effect of alpha interferon treatment in patients with hepatitis B e antigen positive chronic hepatitis B.A meta-analysis [J]. Ann Int Med,1993,119: 312-323

[17] LOK ASF. Treatment of chronic hepatitis B [J].J Viral Hepatitis, 1994,1:105-124

[18] TORRESI J,LOCARNINI S. Antiviral chemotherapy for the treatment of hepatitis B virus infection [J].Gastroenterology,2000,118 (2 Suppl 1):S83-S103

[19] 杨创国，于乐成，陈金军，等.1686 例慢性乙型肝炎中 HBeAg 阴性与阳性患者临床和病毒学特点比较分析[J].中华内科杂志,2005,44(9):648 -651
Yang Chuan-guo,Yu Le-cheng,Chen Jin-jun,et al. A comparison of clinical and virological characteristics of 1686 cases of HBeAg-negative and HBeAg-positive chronic hepatitis B[J]. Chinese Journal of Internal Medicine,2005,44(9):648-651

[20] 姚光弼，计焱焱，周霞秋，等.双环醇治疗慢性丙型肝炎的临床研究[J].中华医学杂志，2002,82(14):958-960.
Yao Guang-bi,Ji Yan-yan,Zhou XIa-qiu,et al.Treatment of chronic hepatitis C by bicyclum, a randomized double-blind placebo controlled trial [J].National Medical Journal of China，2002,82(14): 958-960