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焦点论坛 TOPIC HIGHLIGHT

HBV/HCV重叠感染的抗病毒治疗

谭友文

■背景资料
HBV/HCV重叠感染可以加速肝脏疾病的发展, 更易发展为肝硬化和肝细胞癌, 对于感染造成肝纤维化、肝硬化或有发展肝细胞癌危险因素的患者建议抗病毒治疗, 对重叠感染的治疗, 需根据不同的临床模式进行评估, 采用不同的治疗方案. 但在治疗前后均需监测HBV和HCV病毒学指标和生化学指标的变化. 防止“优势”模式的转换而出现肝炎的复发.

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Antiviral treatment of hepatitis B virus and hepatitis C virus co-infection

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Abstract
Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are among the most common causes of advanced chronic liver disease worldwide. HBV/HCV co-infection is not uncommon with an estimated 7–20 million individuals affected worldwide. Patients with HBV/HCV co-infection have an increased risk of cirrhosis, hepatocellular carcinoma (HCC), and even death. The pathophysiology of HBV/HCV co-infection is complex, as different patterns of virological dominance may occur, which can even fluctuate over time. Recently, combination of pegylated interferon (PEG-IFN) plus ribavirin has been explored in HBV/HCV-coinfected patients who are positive for HCV-RNA. In this paper, we summarize the epidemiology, viral interaction and clinical features of HBV/HCV co-infection and the available treatment options. Detailed serological and virological evaluations are required for HBV/HCV-co-infected patients before initiation of antiviral therapy. At present, PEG-IFN-a plus ribavirin should be the treatment of choice in patients with dominant HCV replication. However, HBV rebound may occur after elimination of HCV, and thus close monitoring for both viruses is recommended even for patients with initially suppressed HBV DNA.

Key Words: Hepatitis B virus; Hepatitis C virus; Infection

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摘要
从全球范围看, 乙型肝炎病毒(hepatitis B virus, HBV)和丙型肝炎病毒(hepatitis C virus, HCV)重叠感染估计约有700-2000万人口感染. 重叠感染和单一HBV或HCV感染比较, 更易发展为肝硬化、肝细胞癌甚至肝衰竭的比例也高, HBV和HCV重叠感染可有四种不同的临床模式, 即HCV活动伴HBV非活动, HBV活动伴HCV非活动, HBV与HCV混合感染, HBV与HCV病毒均不可测, 对重叠感染的治疗, 需根据不同的临床模式进行评估, 采用不同的治疗方案, 治疗前后均需监测HBV和HCV病毒学指标和生化学指标的变化. 防止“优势”模式的转换而出现肝炎的复发.

关键词: 乙型肝炎病毒; 丙型肝炎病毒; 感染

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0 引言
乙型肝炎病毒(hepatitis B virus, HBV)和丙型肝炎病毒(hepatitis C virus, HCV)是两种可以导致慢性肝炎、肝硬化甚至肝细胞癌的病毒, 全球范围看, 慢性乙肝感染者有3.5亿, 慢性丙肝感染者有1.3亿[1,2]. 那两者的重叠感染必然成为不可回避的事实. 从现有文献看, 两者的重叠感染较单一感染有更大的发展成肝硬化、肝细胞癌的风险[3,4], 由于两种病毒的相互作用, 使HBV/

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HCV重叠感染的治疗要远复杂于HBV和HCV的单一感染, 理想的抗病毒治疗是两种病毒都能清除, HBV/HCV重叠感染的治疗和单一感染抗病毒治疗, 需要在抗病毒前进行评估, 即何种病毒起主导作用或者说, 对肝脏的损害以哪种为主. 我国是HBV高发区, 同样也是HCV感染高发区, HBV/HCV重叠感染众多, 急需规范化的诊疗指南推荐, 但有关HBV/HCV混合感染的研究却很少, 尤其关于自然史、感染的治疗结果等都是需要迫切了解的问题. 作者复习近年关于HBV/HCV重叠感染的文献资料, 对HBV/HCV重叠感染的研究现状进行总结, 对临床工作有一定的指导作用.

1 流行病学

HBV/HCV重叠感染并不少见, 多流行在乙肝高发区, 如亚洲、非洲和南美[5-7], 在低流行区感染人口约0.9%-5%[8], 在一些高流行区, 甚至超过25%, 全球HBV/HCV混合感染人口约700-2 000万, 在我国台湾地区感染率约0.4%-2.0%, 大陆和香港地区感染率约0.60%-1.74%, 在慢性携带者发现约有11.4%-14.5%患者抗HCV阳性[9-12]. 感染人群主要集中在静脉毒品使用者、AIDS患者、多脏器损伤、血透以及不洁血制品使用者[13,14]. HBV/HCV重叠感染的实际人数可能远高于报道的, 由于隐匿性乙肝(HBV DNA阳性, 但HBsAg阴性)的存在. HBV/HCV混合感染受关注的主要是由于可能导致严重肝脏疾病和增加肝细胞癌的风险[15,16], 台湾一份12 008例居民10年的随访资料显示, HBV/HCV重叠感染者和单纯HCV感染比较有更大的肝细胞癌风险(4.46%比2.98%). Liaw等也证明了HBsAg阳性携带者伴HCV重叠感染, 与慢性乙肝比较更易肝硬化和肝细胞癌(31.3% *vs* 17.2%; 9.4% *vs* 4,7%). 更多文献证实了HBV/HCV重叠感染不仅增加肝细胞癌的风险, 更是增大了与肝病相关的疾病死亡[3,17-19].

1.1 隐匿性HBV与HCV重叠感染 隐匿性HBV是指血清HBV DNA持续阳性, 但HBsAg阴性的乙肝患者[20,21], 在慢性丙肝经常发现隐匿性HBV的存在[22], 尤其在亚洲[22,23]、南欧特别是意大利近1/3慢性丙肝发现乙肝病毒复制, 但HBsAg阴性[24,25]. 这种混合感染认为更易发展成肝硬化并且干扰素的治疗效果也差[24,26-30]. 可是也有文献认为, HBV感染是否活动与肝炎的临床转归和严重程度无关[31,32]. 因此, 隐匿性HBV与HCV混合感染的流行病学资料仍需要严格的列队研究.

1.2 HBV与HCV混合感染 HBV与HCV混合感染或者同时感染, 文献报道并不多, 文献第1例是由Liaw等报道的, 这是一个针刺的意外暴露病例[33], 6 wk内获得了血清学的证实. 另1例是由于输血后感染的, Baginski等[34]也迅速发现了HBs的血清转换. 因此认为HBV的清除或低水平表达与HCV有关. 可Alberti等认为两种病毒的混合感染和单一HBV或HCV的病毒清除并无多大关系.

在HBV流行地区, 慢性HBV携带和HCV重叠感染更多见[23,35], 文献认为慢性HBV携带感染上急性丙肝, 有更高的重症化倾向和死亡率[36,37]. 相反的资料认为, 急性丙肝的感染可以有助于HBV的暂时和永久性消失[38]. Liaw等[16]发现, 发生在慢性HBV的慢性HCV和单一慢性HCV比较, 10年发展成肝硬化的患者为48%, 20年后发展成肝癌为32%, 显然更高. 和HCV感染在HBV患者相比, 急性HBV感染在慢性HCV的发生更少. 这样的病例往往发生在特殊的人群, 如静脉药瘾者, 多性伴者.

2 病毒的相互作用

HBV与HCV病毒之间的相互作用如何? 从HBV流行区的观察来看, HBV/HCV重叠感染的个体其HCV RNA水平和单一HCV感染的患者水平相当, 但其HBV DNA水平却比单一HBV感染的患者水平低. 从慢性乙肝混合感染HCV的个体发现, e抗原血清转换甚至HBsAg清除更以发生, 这些资料提示HBV与HCV重叠感染, 更利于HBV的抑制, 并认为HBV的复制受到了HCV的抑制. 这个结果可以解释, 在HBV高流行区, 为什么隐形乙肝多见于伴有HCV感染者. 同样的, 在以HCV感染为“优势”的重叠感染中, 伴有HBV高复制的患者比低水平的, 其HCV RNA往往更低. 所以认为, 这两种病毒相互抑制, 当一种病毒处于活动状态(HCV RNA>50 000 kIU/L; 或HBV DNA>2 000 kIU/L), 而另一种病毒往往处于抑制状态(HCVRNA阴性或HBV DNA阴性或<2 000 kIU/L). 并且发现在肝组织HBV DNA聚合酶, HBsAg和HBcAg表达下降[5,39-41]. 急性HCV感染不仅抑制HBV DNA, 而且促进HBe血清学转换, 甚至HBsAg清除[42,43].

HBV与HCV重叠感染最少有4种临床模式, HCV活动伴HBV非活动, HBV活动伴HCV非活动, HBV与HCV混合感染, HBV与HCV病毒均不可测, 在我国大多表现为HCV活动伴HBV非活

■研发前沿
重叠感染如果以丙肝为优势感染, Peg-干扰素与利巴韦林应该为首选, 如果乙肝优势感染的, 是否需要加用核苷类似物, 仍需要更多的临床数据.

■相关报道
Liaw等也证明了HBsAg阳性携带者伴HCV重叠感染, 与慢性乙肝比较更易肝硬化和肝细胞癌.

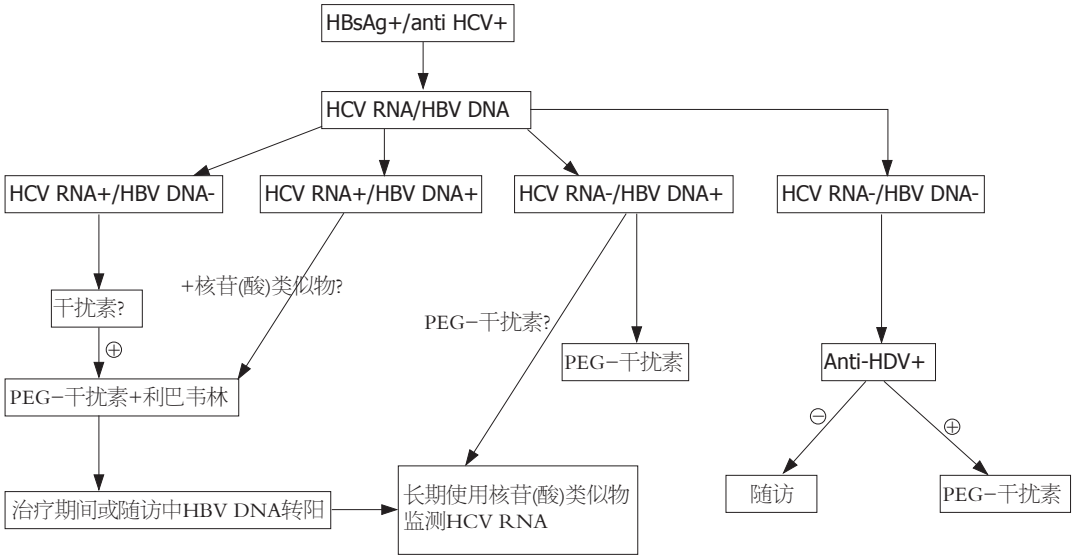

图 1 HBV/HCV重叠感染的抗病毒治疗的建议. 在不同时间段至少检查2次.

动. 现有的大多数资料未充分考虑病毒的不同模式. 一份来自以色列的多中心资料对不同的重叠感染模式进行了长期的随访, 共有133例未进行治疗的HBV与HCV重叠感染患者, 分别属于上述4种病毒学模式, 经过1-2年的随访, 发现约32例(31%)在动态观察中出现了模式的转变, 这种现象的存在, 是在临床进行治疗前需要评估的. 在抗病毒治疗过程中, 两种病毒间的相互作用以至优势模式的转变是不得不关注的. 如丙肝病毒被抗病毒抑制, 也许乙肝病毒会再燃甚至导致严重的肝炎发作[44,45].

但是病毒之间的这种相互作用机制却知道甚少, HBV和HCV均为嗜肝病毒, 两者单独感染机体均可以引起特异体液免疫和细胞毒T淋巴细胞反应, HBV往往引起的反应强烈, 可以清除HBV并免疫损伤肝细胞, 而HCV由于其表位的高度突变性, 免疫反应较弱, 也正是如此HCV感染易慢性化, 相反, 肝损伤也较轻. 那HBV和HCV同时感染肝细胞, 为什么两者似乎相互抑制? 早期体外研究显示, 在Huh-7细胞同时感染HBV和HCV, 可见HCV肝炎核心蛋白抑制HBV-DNA的转录. 但新的研究认为HBV和HCV在肝细胞混合感染并相互抑制是不可能的[46,47]. 机体对病毒的不同免疫反应更让人信服.

3 HBV/HCV重叠感染的抗病毒治疗

HBV/HCV重叠感染治疗的首要目的仍是持续和长久地抑制和清除HBV/HCV病毒, 减少肝组织的炎症反应, 阻止肝纤维化的发展, 最终减少肝硬化及肝细胞癌的发生, 达到延长寿命[48]. 由于HBV/HCV重叠感染的抗病毒治疗数据的有限, 目前还没有对这种特殊感染状态的抗病毒指南[49]. 个体化治疗是治疗准则, 对病毒学特点、曾经的抗病毒治疗史以及是否伴有其他病毒的感染如HDV、HIV等均需考虑. 我们复习文献, 对HBV/HCV重叠感染的抗病毒治疗的建议如图1. 治疗慢性乙肝的药物有干扰素、Peg-干扰素、拉米夫定、阿德福韦、恩替卡韦、替比夫定和替诺福韦. 慢性丙肝的治疗药物干扰素、Peg-干扰素与利巴韦林.

3.1 干扰素(加利巴韦林) 干扰素对两种病毒均有抑制作用, 干扰素治疗HBV和HCV的文献很多, 但对混合感染治疗的经验却很少, 总之, 常规治疗剂量对混合感染的疗效很差, 但如果提高使用剂量, 900万, 3次/wk, 可以明显提高HCV RNA的清除, HBeAg的转换或HBV DNA的抑制[50]. 干扰素与利巴韦林治疗HBV/HCV重叠感染, 据报道的几篇文献看[51-53], 24 wk HCV RNA的持久应答率43%-69%, HBV DNA不可测达11%-35%. 但HBsAg消失率1年可达14%, 2年后到21%.

3.2 干扰素加拉米夫定 干扰素加拉米夫定治疗HBV/HCV重叠感染,目前仅见1篇文献报道[54], 8例患者均为HBeAg、HBV DNA、 HCV RNA阳性, 使用500万干扰素和拉米夫定100 mg/d, 治疗12 mo, HCV RNA转阴4例, HBeAg消失3例, 血清转换2例, 3例HBV DNA不可测. 可以看到, 干扰素和核苷(酸)类似物联用可以使用于HBV“优势”的HBV/HCV重叠感染, 但例数尚少, 拉米夫定不是最佳的HBV抑制药物, 其他核苷(酸)类似物可能也可以使用于重叠感染, 尤其推荐

HBV“优势”型的重叠感染或干扰素使用后出现的HBV DNA反弹.

3.3 Peg-干扰素与利巴韦林 Peg-干扰素与利巴韦林是治疗慢性丙肝的金标准药物, 对慢性乙肝HBV DNA的持久应答率也有20%-30%. 这两种药物也常是HBV/HCV重叠感染的治疗选择[54,55], 一份多中心的临床试验显示[56], 19例HBV/HCV混合感染患者, 均为HCV优势感染, 其中13例HBV DNA不可测水平, 10例为HCV基因1型, 所有患者治疗48 wk, 14例获得了HCV RNA应答. 在6例HBV DNA阳性中2例转变为不可测, 2例病毒量下降, 2例保持阳性. 需要注意的是, 原来13例HBV DNA不可测水平的患者中有4例转阳, 这4例均有HCV RNA转阴(<2 000 kIU/L), 其中1例HBV DNA 5.0×10^9 IU/L. 但这几例病毒学反跳没有出现生化学反弹. 一份来自台湾的多中心资料显示[54], 161例混合感染者接受Peg-干扰素与利巴韦林治疗, 疗程结束, HCV基因1型的有72%获得了HCV病毒学应答, 83%非HCV基因1型获得了HCV病毒学应答, 56%的患者同样也获得了HBV病毒学应答. 来自我国一份资料显示, 使用Peg-干扰素与利巴韦林治疗50例HBV/HCV重叠感染, 其中46例认为是HCV优势型, 4例为HBV优势型, 发现24 wk对基因1型的HCV RNA的早期应答(50.0%, 15/30)要远好于单一的HCV感染(16.0%, 4/25); 但HCV RNA的反跳又远高于单一的HCV感染(55.6%, 15/27: 21.4%, 3/14). 同样看到, 两者间的远期应答却无差异(40.0%, 12/30: 44.0%, 11/25). 并注意到, 联合治疗的副作用, 重叠感染要高于单一感染(30%, 15/50: 13%, 6/46)[57].

目前的文献认为, 重叠感染如果以丙肝为优势感染, Peg-干扰素与利巴韦林应该为首选, 如果乙肝优势感染的, 是否需要加用核苷类似物, 仍需要更多的临床数据.

4 结论

HBV/HCV重叠感染可以加速肝脏疾病的发展, 更易发展为肝硬化和肝细胞癌, 对重叠感染引起的肝衰竭不建议抗病毒治疗, 而推荐肝移植. 对于感染造成肝纤维化、肝硬化或有发展肝细胞癌危险因素的患者建议抗病毒治疗, 治疗方案可以选用Peg-干扰素与利巴韦林加或不加乙肝病毒抑制药物. 两种病毒间的相互抑制作用可能贯穿始终. 在抗病毒前, 对患者血清病毒学和生化学要进行至少3-6 mo的监测, 并评价“优势感染”病毒, 根据上文的推荐选择抗病毒方案. 在治疗期间和停药后6 mo, 应该严密监测血清病毒学和生化学指标, 因为少数文献报道, 在治疗期间和停药后出现了肝炎的发作.

对于HBV/HCV重叠感染抗病毒治疗, 我们仍然知之甚少, 如对抗病毒疗效是否存在地域性差距, 对干扰素的应答是否和HBV, HCV单一感染一样, 核苷(酸)类似物的加用能否抑制HBV的反弹等.

■同行评价
本文选题准确, 有一定临床参考价值.

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本刊讯 《中国学术期刊评价研究报告-RCCSE权威、核心期刊排行榜与指南》由中国科学评价研究中心、武汉大学图书馆和信息管理学院联合研发, 采用定量评价和定性分析相结合的方法, 对我国万种期刊大致浏览、反复比较和分析研究, 得出了65个学术期刊排行榜, 其中《世界华人消化杂志》位居396种临床医学类期刊第45位. (编辑部主任: 李军亮 2010-01-08)