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在线投稿: http://www.baishideng.com/wcjd/ch/index.aspx
帮助平台: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.11569/wcjd.v23.i27.4368

世界华人消化杂志 2015年9月28日; 23(27): 4368-4375
ISSN 1009-3079 (print) ISSN 2219-2859 (online)


文献综述 REVIEW

# 慢性丙型肝炎基因1型抗病毒治疗的进展

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**背景资料**
丙型肝炎病毒(hepatitis C virus, HCV)基因1型被公认为是“难治型”, 对乙二醇干扰素联合利巴韦林抗病毒治疗疗效欠佳, 亟待更有效的抗病毒药物. 从早期特拉匹韦、博塞波维到Harvoni, VIEKIRA PAK复合制剂, 基因1型抗病毒治疗有了新的突破.

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收稿日期: 2015-07-23 修回日期: 2015-08-19
接受日期: 2015-08-31 在线出版日期: 2015-09-28

## Progress in antiviral treatment of chronic hepatitis C virus genotype 1 infection

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Received: 2015-07-23 Revised: 2015-08-19
Accepted: 2015-08-31 Published online: 2015-09-28

## Abstract
Hepatitis C virus (HCV) genotype 1 infection is difficult to treat, and the efficacy of peginterferon-α (PEG-IFN-α) and ribavirin (RBV) combination therapy is not very satisfactory. In recent years, direct-acting antiviral drugs (DAAs) have been developed and licensed for the treatment of HCV infection. The first-generation DAAs are NS3/4 polymerase inhibitors, which are often used in combination with PEG-IFN-α and RBV. Subsequently, some IFN-free regimens of NS5A inhibitors and NS5B polymerase inhibitors have shown promising results. Harvoni and VIEKIRA PAK have been approved by the United States Food and Drug Administration. These regimens have excellent response rates, short-duration and minimal toxicities and will bring hope to patients who are difficult to cure or with contraindications to the use of RBV or PEG-IFN-α.



Key Words: Hepatitis C; Genotype 1; Antiviral; Small molecular compounds

Deng L, Wang XH. Progress in antiviral treatment of chronic hepatitis C virus genotype 1 infection. Shijie Huaren Xiaohua Zazhi 2015; 23(27): 4368-4375 URL: http://www.wjgnet.com/1009-3079/23/4368.asp DOI: http://dx.doi.org/10.11569/wcjd.v23.i27.4368

## 摘要
丙型肝炎病毒(hepatitis C virus, HCV)基因1型感染患者为难治型, 聚乙二醇干扰素联合利巴韦林标准方案疗效欠佳. 近来, 直接抗病毒药物研制成功, 陆续上市. 第一代以NS3/4A蛋白酶抑制剂为主, 但其仍需联合聚乙二醇干扰素及利巴韦林. 随后, 以NS5A抑制剂, NS5B聚合酶抑制剂为主的无干扰素方案陆续出现. Harvoni, VIEKIRA PAK等复合制剂已获得食品药品监督管理局(Food and Drug Administration, FDA)批准上市, 这种高疗效、短疗程、不良反应小的直接抗病毒方案, 为难治型患者和有干扰素及利巴

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**关键词: 丙型肝炎; 基因1型; 抗病毒; 小分子化合物**

**核心提示:** 小分子化合物直接抗病毒打破了标准治疗方案(standard of care)依赖干扰素、利巴韦林的局限. 本文着重介绍了NS3/4A、NS5A、NS5B等小分子化合物联合治疗丙型肝炎病毒基因1型. 这些高效、短疗程、不良反应小的无干扰素方案为丙型肝炎患者带来福音.

邓玲, 王小红. 慢性丙型肝炎基因1型抗病毒治疗的进展. 世界华人消化杂志 2015; 23(27): 4368-4375 URL: http://www.wjgnet.com/1009-3079/23/4368.asp DOI: http://dx.doi.org/10.11569/wcjd.v23.i27.4368

## 0 引言

慢性丙型肝炎(chronic hepatitis C, CHC)在世界范围内感染人数已经超过1.8亿, 每年新发感染人数约3-4百万[1]. 其中基因1型感染者占绝大部分, 约40%-80%[2,3]. 然而, 基因1型抗病毒治疗的疗程长, 疗效欠佳, 复发率高, 被公认为是“难治型”[4]. 近年, CHC基因1型抗病毒治疗研究有了很大进展, 本文对此做一系统概述.

## 1 干扰素依赖的抗病毒方案

1.1 聚乙二醇干扰素 20世纪早期, 聚乙二醇干扰素-α(polyethylene glycol-interferon-α, PEG-IFN-α)联合利巴韦林(ribavirin, RBV)成为CHC的标准治疗方案(standard of care, SOC), PEG-IFN-α 2a/PEG-IFN-α 2b, 1次/wk, 联合RBV(800-1200 mg/d), 48 wk, 持续病毒学应答(sustained virologic response, SVR)约为40%-50%. 随后研究[5,6]发现年龄<65岁, 白介素-28B(interleukin, *IL-28B*)基因rs12979860 CC型, 基线丙型肝炎病毒(hepatitis C virus, HCV)-RNA水平<$6\times10^5$ IU/mL及无肝硬化这类患者的SVR率可以提高到60%. 然而, 仍有一些患者疗效不佳, 文献[7]报道其治疗无应答率20%, 复发率26.6%, 因不良反应终止治疗的发生率为10.4%, 不良反应主要见于神经系统, 血液系统及皮肤[8]. 此外, 一些患者具有使用IFN及RBV的禁忌症, 如移植、肾透析、肝硬化等患者.

1.2 小分子化合物 第一代抗HCV的小分子化合物是基于IFN基础上的NS3/4A蛋白酶抑制剂. 研究[9,10]显示靶向直接抗病毒方案(specific target therapy for Hepatitis c, STAT-C)可以有效提高治愈率, 缩短疗程, 减少不良反应; 影响疗效的主要因素有肝脏基础疾病(肝纤维化程度, 有无肝硬化)、基因型、基线HCV RNA水平; 而耐药相关变异(resistance-associated variants, RAVs), *IL28B*基因多态性不作为评估疗效的首要指标.

1.2.1 特拉匹韦/博塞泼维: 特拉匹韦(Telaprevir, TVR)和博塞泼维(Boceprevir, BOC)为第一代NS3/4A丝氨酸蛋白酶抑制剂, 2011年在美国获得食品药品监督管理局(Food and Drug Administration, FDA)批准上市. 适用于基因1型代偿期肝硬化、SOC无应答者, 方案为TVR/BOC+PEG-IFN(P)+RBV(R)三联治疗[11]: TVR 750 mg, 3次/d, 前12 wk为三联治疗(TVR-PR), 后12 wk是PEG-IFN+RBV(PR)维持治疗, 总疗程24 wk; BOC 800 mg, 3次/d, 前4 wk单独使用PR, 之后BOC-PR继续治疗24 wk, 总疗程28 wk. III期临床试验报道[12-14], TVR/BOC-PR的SVR为66%-75%, 然而, 来自临床实践中的报道显示[15]其有效率略减(TVR组53%, BOC组40%). 治疗终止率TVR为43.4%, BOC为47.1%, 因无应答终止治疗的患者TVR组占6.1%, BOC组占26.8%, 因病毒学失败终止治疗者TVR组为16%, BOC组为4.9%. TVR的RAVs主要是V36M、R155K, 而BOC是T54A[16]. 常见不良反应包括: 严重贫血、抑郁、厌食、皮疹、细菌感染等[17]. 此外, TVR/BOC-PR方案价格较昂贵, TVR 750 mg为100美元, BOC 800 mg为34美元. TVR/BOC-PR一个周期治疗费用约为24000-28248美元[18].

1.2.2 Simeprevir: Simeprevir(SMV)为第二代NS3/4A蛋白酶抑制剂. 已获FDA批准上市. 适用于基因1型初治、初治复发、初治部分应答或者无应答(包括代偿期肝硬化)患者. 治疗方案为SMV 150 mg/d, 联合PR[19-21]. 初治、初治复发者总疗程为24 wk, 初治部分应答或者无应答者需延长疗程至48 wk, 不良反应也随之增加. 值得注意的是NS3蛋白酶序列Q80K变异的基因1a型感染患者耐药性增加, 不采用该联合方案[22]. SMV与TVR有效性与安全性的多项研究分析证明SMV较TVR获得SVR率更高, 且

**研发前沿**
以Sofosbuvir为代表的无干扰素治疗方案为丙型肝炎抗病毒治疗打开一片新天地. 各型HCV的有效率、病毒耐药、药物不良反应仍是研究重点.

**相关报道** Sofosbuvir+Ledipasvir治疗方案对基因1型初治患者治疗12 wk持续病毒学应答(sustained virologic response, SVR)高达为99%, 有肝硬化经治患者, 治疗24 wk SVR为97%, 对初治无肝硬化者甚至可以缩短疗程至8 wk. 该方案不仅有效率高, 不良反应小, 还可以用于HCV/人类免疫缺陷病毒(human immunodeficiency virus, HIV)合并感染者.

不良反应低, 患者更易耐受, 但皮疹、皮肤瘙痒症状较TVR更明显[23].

## 2 不依赖IFN的抗病毒方案

2.1 小分子化合物 以小分子化合物为首的无IFN方案陆续上市, 除了NS3/4A蛋白酶抑制剂, NS5A抑制剂、NS5B聚合酶抑制剂也是研发热点. 研究发现[24,25]NS5B聚合酶抑制剂可以达到较高的有效性及安全性, 而耐药性则是最低的, 被认为是最具“潜力”的小分子化合物. 除了Sofosbuvir(SOF)单药联合RBV可用于基因2、3型外, 基因1型治疗主要还是两种及以上小分子化合物联用, 其原理为同时作用于不同位点, 提高疗效, 减少耐药.

2.1.1 SOF+Ledipasvir方案: SOF为NS5B聚合酶抑制剂, 其重要RAVs为S282T, 该突变可以减弱SOF抗病毒敏感性. Ledipasvir(LDV)为NS5A抑制剂. 对CHC基因1a、1b型均表现出很强的抗病毒活性, 并且可以有效地抑制S282T突变. 治疗方案[26]为: LDV 90 mg, 1次/d+SOF 400 mg, 1次/d(LDV-SOF). 适用于基因1型初治、经治、有/无肝硬化患者. 肝硬化是影响疗程的一项重要因素, 对于无肝硬化(包括初治、经治)疗程为12 wk, 代偿期肝硬化(包括初治、经治)可联合RBV治疗12 wk, 若有RBV使用禁忌或者不能耐受者, 可LDV-SOF方案延长至24 wk; 无肝硬化、基线HCV RNA<$6\times10^7$ IU/mL者, 可缩短疗程至8 wk. 但对肝纤维化3级(F3)的患者需严密监测HCV RNA水平[24]. ION-Ⅰ、Ⅱ、Ⅲ期临床研究[27-29], 初治患者治疗12 wk SVR为99%, 经治患者治疗12 wk的SVR为94%, 初治患者治疗8 wk SVR为94%. SIRIUS-Ⅱ主要观察肝硬化经治患者, 治疗24 wk SVR为97%[30]. 其常见不良反应为鼻咽炎(29.2%)、头痛、心神不宁[31]. 使用SOF期间需监测肾功能, 对于eGFR<30 mL/(min•1.73 $m^2$)者, SOF的最佳剂量尚不明确(说明: SVR指治疗结束观察12 wk, HCV RNA持续低于检测值. 文献[32]报道, 对小分子化合物直接抗HCV, 治疗结束观察12 wk与观察24 wk得到疗效的有效性是相似的). 对特殊感染人群: HCV/人类免疫缺陷病毒(human immunodeficiency virus, HIV)共感染者SVR为98%, 且不会增加HIV病毒载量, 对抗逆转录病毒药物的活性没有明显影响[33]. 常见不良反应为鼻充血、肌痛. 肝硬化肝移植前患者1a型SVR为89%, 1b型为100%[34]. LDV-SOF方案相较SOF单独治疗, 大大地减少了耐药的发生. 2014-10-10, Harvoni(LDV-SOF)复合制剂获FDA批准上市, 该药物是第一个批准用于治疗基因1型丙型肝炎感染, 且不需要联合IFN或RBV的全口服抗丙型肝炎治疗方案, 并获得FDA“优先评审”资格, 也是第7个获得“突破性药物”资质的药物. 但价格高昂, 一个12 wk或8 wk疗程的Harvoni在美国预定收费分别为94500和63000美元.

2.1.2 SOF+SMV方案: 治疗方案为: SOF 400 mg, 1次/d+SMV 150 mg, 1次/d(SOF-SMV). 适应症为: 初治、经治者(包括肝硬化). 无肝硬化者SOF-SMV-R方案治疗12 wk, 有肝硬化或者RBV使用禁忌者, SOF-SMV需延长疗程至24 wk[24,35]. COSMOS试验发现, SOF-SMV治疗总SVR率为92%, 其中肝纤维化(F0-F1)经治组SVR为90%, 肝纤维化(F3-F4)经治或者初治组SVR为94%. 基因1a型基线G80L突变者SVR为93%, 无G80L突变组SVR为97%. 常见不良反应为疲乏、头痛、恶心. 有4例(占2%)因不良反应停止治疗[36]. 该方案已推荐用于临床治疗.

2.1.3 Paritaprevir+Ritonavir(ABT-450/r)+Ombitasvir+Dasabuvir方案: Paritaprevir(ABT-450)为非结构性NS3/4A蛋白酶抑制剂, 与Ritonavir连用(ABT-450/r)可增加ABT-450的血浆半衰期. Ombitasvir为NS5A复合物抑制, Dasabuvir为非核苷类NS5B RNA聚合酶抑制剂[37,38].

欧洲肝脏病学会(European Association for the Study of the Liver, EASL)指南推荐治疗方案为: ABT-450 12.5 mg, 2次/d+Ritonavir 50 mg, 2次/d+Ombitasvir 75 mg, 2次/d+Dasabuvir 250 mg, 2次/d+RBV(3D-R), 疗程12 wk. 适用于初治、经治者(包括肝硬化). 基因亚型、有无肝硬化是决定疗程和是否联合RBV治疗的关键因素. 1a型有肝硬化者3D-R方案需延长至24 wk[24]. SAPPHIRE-Ⅰ、Ⅱ临床试验按ABT-450 150 mg, 1次/d+Ritonavir 100 mg, 1次/d+Ombitasvir 25 mg, 1次/d+Dasabuvir 250 mg, 2次/d+RBV(3D-R)的方案进行研究, 治疗12 wk SVR率>95%. 其中, 初治无肝硬化组, 1a型SVR为95%, 1b型为98%, 病毒学失败和复发者分别占0.2%和1.5%; 经治无肝硬化组, 1a型SVR为96%, 1b型为97%[39,40]. TURQUOISE-Ⅱ临床试验证明对代偿期肝硬化患者3D-R方案治疗12 wk SVR为92%, 24 wk为96%. 虽然3D-R方

**表 1 不依赖干扰素的抗病毒方案**

| 方案 | 阶段 | 适应症 | 疗程 | SVR率 | 不良反应 |
|---|---|---|---|---|---|
| Sofosbuvir+Ledipasvir+/RBV | Harvoni复合制剂已上市 | 基因1型初治, 经治, 有/无肝硬化者, HCV/HIV共感染者, 肝硬化肝移植前患者 | 8、12、24 wk | 94%-100% | 贫血、头痛、乏力、鼻咽炎、头痛、心神不宁 |
| | ION-ⅠⅡⅢ | 基因1型初治, 经治者(包括肝硬化) | 8、12、24 wk | 94%-99% | 同上 |
| | SIRIUS-Ⅱ | 基因1型肝硬化经治者 | 12、24 wk | 96%-97% | 同上 |
| Sofosbuvir+ Simeprevir+/RBV | COSMOS | 基因1型初治, 经治者(包括肝硬化) | 12、24 wk | 90%-97% | 疲乏、头痛、恶心 |
| Paritaprevir+Ritonavir+Ombitasvir+Dasabuvir+/RBV | VIEKIRA PAK为复合制剂已上市 | 基因1型初治,经治者(包括肝硬化) | 12、24 wk | | 疲乏、头痛、恶心、呕吐 |
| | SAPPHIRE-ⅠⅡ | 初治, 经治者(包括肝硬化) | 12、24 wk | 95%-98% | |
| | TURQUOISE-Ⅱ | 代偿期肝硬化 | 12、24 wk | 92%-96% | |
| Grazoprevir+Elbasvir+/RBV | C-WORTHY-Ⅱ | 代偿期肝硬化初治, 经治患者, HCV/HIV共感染者 | 12、24 wk | 87%-97% | 疲乏、头痛、恶心、轻度贫血、ALT/AST轻度升高 |
| Daclatasvir+Asunaprevir | HALLMARK-DUAL-III | 基因1b型初治, 经治, 有干扰素使用禁忌者 | 12、24 wk | 82%-90% | 头痛、恶心、腹泻 |
| Daclatasvir+Asunaprevir+Beclabuvir | UNIT-ⅠⅡ | 无/代偿期肝硬化(包括初治, 经治者) | 12、24 wk | 85%-100% | 同上 |

SVR: 持续病毒学应答; HCV: 丙型肝炎病毒; HIV: 人类免疫缺陷病毒; ALT: 丙氨酸转氨酶; AST: 谷草转氨酶.

**创新盘点**

本文以指南为根据, 查阅近年丙型肝炎抗病毒治疗药物的发展, 总结归纳为干扰素依赖和不依赖干扰素的抗病毒方案二部分. 其中, 不依赖干扰素抗病毒方案是重点, 列举的方案具有代表性.

案SVR率很高, 但至少4种药物的联合使用, 不良反应明显. 不良反应的发生率为91.3%, 因不良反应停止治疗者占2.1%, 其中疲乏、头痛、恶心、呕吐等较为常见[41]. VIEKIRA PAK为复合制剂, 含1片Ombitasvir 75 mg+Paritaprevir 12.5 mg+Ritonavir 50 mg的复合制剂和1片Dasabuvir 250 mg, 已经在国外上市.

2.1.4 Grazoprevir+Elbasvir方案: Grazoprevir为第二代NS3/4A蛋白酶抑制剂, Elbasvir为NS5A抑制剂. 治疗方案为: Grazoprevir 100 mg, 1次/d+Elbasvir 50 mg, 1次/d, 疗程为12 wk或者24 wk. 适用于代偿期肝硬化初治、经治患者. C-WORTHY-Ⅱ期临床试验发现: 总SVR率为(240/253)95%. 加入RBV及延长疗程未见明显优势. 常见不良反应为疲乏79%、头痛58%、恶心14%、轻度贫血4%、谷丙转氨酶(alanine transaminase, ALT)/谷草转氨酶(aspartate transaminase, AST)轻度升高2%[42]. 该方案的优势在于对肝硬化代偿期、初治失败患者的SVR率均>90%. 另一优势是对于HCV/HIV共感染患者, SVR率可以达到87%-97%, 且不良反应小[43]. 但仍处于临床III期试验阶段.

2.1.5 Daclatasvir+Asunaprevir方案, Daclatasvir+Asunaprevir+Beclabuvir方案: Daclatasvir(DCV)为NS5A抑制剂, Asunaprevir(ASV)为NS3蛋白酶抑制剂. HALLMARK-DUAL临床III期试验, 对基因1b型初治、经治、有IFN使用禁忌者, 给予DCV 60 mg, 1次/d+ASV 100 mg, 2次/d, 初治组疗程12 wk, 其余组疗程24 wk. 试验发现, 初治组SVR率为90%, 经治组SVR率为82%, 有IFN使用禁忌组SVR率为82%[44]. DCV-ASV方案较其他无IFN方案无显著疗效优势. 随后又加入Beclabuvir, 为非核苷类NS5B聚合酶抑制剂. 即DCV-TRIO治疗方案: DCV 30 mg+ASV 200 mg+Beclabuvir 75 mg(DCV-TRIO), 2次/d. UNIT-Ⅰ、Ⅱ期临床试验分别对无肝硬化、代偿期肝硬化(包括初治、经治者)进行研究, 初治组: 无/有代偿期肝硬化SVR率分别为92%、93%, 经治组: 无/有代偿期肝硬化SVR率为89.3%、87%, 基因1a型SVR率为85-97%, 基因1b型SVR率为98%-100%, 病毒学失败率为8%, 复发率为5%. 常见不良反应为头痛、恶心、腹泻. 该方案治疗基因1b型疗效明显, 但仍处于临床试验阶段[45,46](表1).

**应用要点**

本文为基因1型有干扰素或利巴韦林使用禁忌症的患者, 标准治疗方案效果欠佳的患者提供一定指导意义. 虽然小分子化合物新上市, 价格昂贵, 但仍然期待在我国的使用.

## 3 MicroRNA

MicroRNA(miRNA)是非编码单链小分子RNA, 可与mRNA的3'端结合, 在胞浆中形成RISC复合体使mRNA降解从而抑制蛋白质的合成[47]. miR-122在肝脏组织中高表达, 与HCV的繁殖与稳定密切相关[48]. Miravirsen是核苷类药物, 以miR-122为作用靶点, 可使成熟的miR-122减少, 稳定异-双倍体, 抑制其功能[49].

Miravirsen主要适用于基因1型, 已进入临床Ⅱ期试验. 36例患者随机分为4组, 分别接受Miravirsen 3、5、7 mg/kg、安慰剂, 皮下注射5 wk后观察18 wk. 结果显示: HCV RNA下降水平与试验药物剂量成正相关. 随着剂量的增加, 没有明显不良反应, 没有检测到基因突变及病毒学逃逸. 除了miR-122, 其他与HCV相关的miRNA, 如: miR-24, miR-149和miR-638等相关研究也正在进行[50,51].

## 4 结论

从SOC到直接抗病毒药物(direct-acting antiviral drugs, DAAs)联合IFN再到无IFN的治疗方案, CHC治疗有了突飞猛进的发展. 就我国而言, 虽然大部分患者为基因1型, 但IL-28B CC的宿主基因型使SOC方案应答率较国外高, 且DAAs新上市, 价格昂贵. 但我们仍然期待高效, 短疗程, 不良反应小的无IFN方案早日进入中国市场, 给迫切需要无IFN治疗的患者带来福音.

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**名词解释**

SVR: 指治疗结束观察12 wk, HCV RNA持续低于检测值. 对小分子化合物直接抗HCV, 治疗结束观察12 wk与观察24 wk得到疗效的有效性是相似的;

耐药相关变异: 是指专由直接抗病毒药物引起的核酸序列的变异, 短期内即可发生, 是导致病毒学突破或者复发的重要因素.

**同行评价**
作者在文中将近年来国内外对慢性丙型肝炎基因1型抗病毒治疗新药物、新方案进行了综述, 选题热门、新颖, 有较高学术价值和临床指导意义.


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编辑: 郭鹏 电编: 都珍珍