·述评·

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慢性乙型肝炎功能性治愈不是梦

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摘要: 慢性乙型肝炎功能性治愈的定义是在停止抗病毒治疗后至少24周,HBsAg<0.05 IU/mL,血清HBV DNA<10 IU/mL。这需要抑制HBV复制、降低病毒抗原产生,同时恢复对HBV感染的免疫应答。约30%~50%接受核苷(酸)类似物治疗并经严格选择的慢性乙型肝炎患者,加用或单用聚乙二醇干扰素α治疗,或经核苷(酸)类似物有限疗程治疗后HBsAg<100 IU/mL者,可获得功能性治愈。目前有40余种新的抗HBV药物和免疫调节剂正在进行临床试验。抑制HBV复制、降低病毒抗原,以及提高HBV感染免疫应答药物的联合应用,可能是慢性乙型肝炎功能性治愈的理想治疗策略。但确定最佳的联合、用药时间、用药顺序和治疗期限等尚需进一步研究。

关键词: 乙型肝炎, 慢性; 乙型肝炎病毒; 功能性治愈; 完全治愈; 抗病毒药

Functional cure of chronic hepatitis B is not a dream

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Abstract: Functional cure of chronic hepatitis B (CHB) is defined as HBsAg<0.05 IU/mL and serum HBV DNA<10 IU/mL for at least 24 weeks after discontinuation of antiviral therapy. This requires suppression of HBV replication and reduction of viral antigen production, as well as restoration of immune response to HBV infection. About 30%—50% of highly selected CHB patients treated with nucleos(t)ide analogues can achieve functional cure after add-on therapy or monotherapy with pegylated interferon-α or a finite course of treatment with nucleos(t)ide analogues among patients with HBsAg<100 IU/mL. At present, clinical trials are being conducted for more than 40 types of novel anti-HBV drugs and immunomodulators. The combination of drugs that inhibit viral replication, reduce antigen burden, and restore immune response to HBV infection may be an ideal strategy to achieve the functional cure of CHB. However, further studies are needed to determine the optimal drug combination, the timing and sequence of medication, and the duration of treatment.

Key words: Hepatitis B, Chronic; Hepatitis B Virus; Functional Cure; Complete Cure; Antiviral Agents

HBV复制率高,每天约产生1万亿个完整的病毒颗粒,以及只含HBsAg的亚病毒颗粒,后者不能复制,也不能感染,但其含量较完整的HBV高1 000~100 000倍[1-2]。血液循环中的大量HBsAg可导致慢性HBV感染者免疫耗竭,而自发、或聚乙二醇干扰素α(PEG-IFN-α)或核苷(酸)类似物[nucleos(t)ide analogues, NAs]治疗后,发生HBeAg或HBsAg消失者可恢复HBV特异性T淋巴细胞免疫应答[3-7]。最近研究显示,小干扰RNA(small interfering RNA, siRNA)治疗后,HBsAg显著下降的患者可恢复HBV T淋巴细胞特异性免疫应答[8],结果提示,至少一部分慢性乙型肝炎(CHB)患者在HBV复制和HBsAg产生被抑制后,HBV特异性T淋巴细胞免疫应答可以恢复。因此,HBsAg消失对HBV特异性T淋巴细胞免疫应答恢复和CHB治愈具有重要意义。

CHB完全治愈(彻底治愈)是指肝细胞中HBV cccDNA和整合的HBV DNA消失。但目前由于无消除cccDNA和

整合HBV DNA的新药、无商品化和标准化检测cccDNA及整合的HBV DNA试剂，很难达到这一治疗目标[8-9]。目前，抗HBV的现有药物和新药临床试验的主要治疗终点是功能性治愈，其定义是：(1)HBsAg<0.05 IU/mL(伴或不伴抗-HBs阳转)；(2)HBV DNA<10 IU/mL；(3)HBeAg血清学转换(伴或不伴抗-HBe阳性)；(4)抗-HBc阳性；(5)ALT<正常值上限(ULN：男30 U/L，女19 U/L)；(6)肝组织学明显改善；(7)持久维持；(8)ccc DNA存在，不活动；(9)整合的HBV DNA存在，但减少；(10)巩固治疗24周；(11)停药后24周上述指标仍维持不变[8-14](图1)。

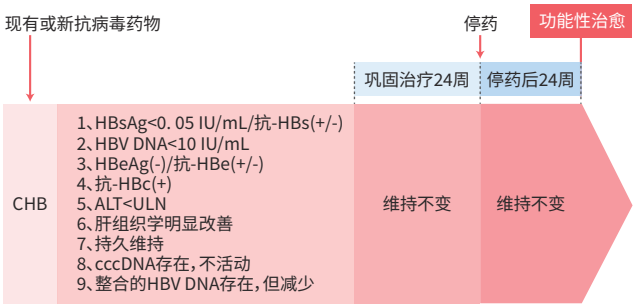

图1 功能性治愈示意图

Figure 1 A sketch map of functional cure

1 现行抗HBV药物的功能性治愈

1.1 *NAs治疗后，对优势人群加用或单用PEG-IFN-α治疗达到功能性治愈* NAs治疗后的所谓优势人群是指：(1)HBV DNA<10 IU/mL；(2)HBeAg血清学转换(抗-HBe阳转)；(3)HBsAg<500 IU/mL；(4)ALT<ULN。对该类CHB患者，加用PEG-IFN-α治疗，基线HBsAg≤100 IU/mL、≤200 IU/mL和≤500 IU/mL的CHB功能性治愈率分别53.02%、30.29%和20.04%；单用PEG-IFN-α治疗，基线HBsAg≤100 IU/mL、≤200 IU/mL和≤500 IU/mL功能性治愈率分别55.84%、27.32%和19.12%[15](图2)。

Gao等[16]检测47例功能性治愈CHB患者的肝内HBV cccDNA和HBV DNA发现，23.4%的患者上述2项指标均为阴性，提示已达到完全治愈(彻底治愈)。

1.2 *应用NAs有限疗程，获得功能性治愈* Hirode等[17]报道一项国际多中心、多人种队列研究(RETRACT-B Study)，对1 552例CHB患者于NAs停药后随访4年，停药时HBsAg水平低的患者HBsAg消失率较高。对于亚洲CHB患者，停药时HBsAg<100 IU/mL和≥100 IU/mL患者的HBsAg消失率分别为33%和2%。对于白人CHB患者，停药时HBsAg<1 000 IU/mL和≥1 000 IU/mL患者的HBsAg消失率分别为41%和5%。因此，对于亚洲CHB患者，NAs治疗至HBsAg<100 IU/mL可停药；对于白人CHB患者，NAs治疗至HBsAg<1 000 IU/mL时可停药。但两者均须在确保密切监测的情况下，方可停药。

一项纳入24篇文献、3 732例CHB患者的荟萃分析结果显示，对于亚洲CHB患者，停药时HBsAg<100 IU/mL者，与停药时HBsAg≥100 IU/mL者比较，其HBsAg消失率高(28.3% vs 2%)、病毒学复发率低(33.4% vs 72.1%)、生化学复发率低(17.3% vs 48.1%)。对于白人CHB患者，停药时HBsAg<1 000 IU/mL患者的HBsAg消失率高于停药时HBsAg≥1 000 IU/mL者(38.4% vs 6.4%)，但其病毒学复发率和生化学复发率均低于停药时HBsAg≥1 000 IU/mL者，分别为52.7% vs 63.8%和15.9% vs 26.4%[18]。

对于亚洲CHB患者，NAs有限疗程的优势人群是：(1)HBsAg<100 IU/mL；(2)HBeAg血清学转换(抗-HBe阳性)；(3)HBV DNA<10 IU/mL；(4)ALT<ULN(男30 U/L、女19 U/L)；(5)巩固治疗至少1年，上述指标维持不变；(6)停药后确保密切监测[7-9,17-20]。NAs有限疗程CHB治疗策略见图3。

NAs治疗有限疗程停药后必须确保密切监测，停药后前3个月，每月检测1次ALT和HBV DNA，之后每

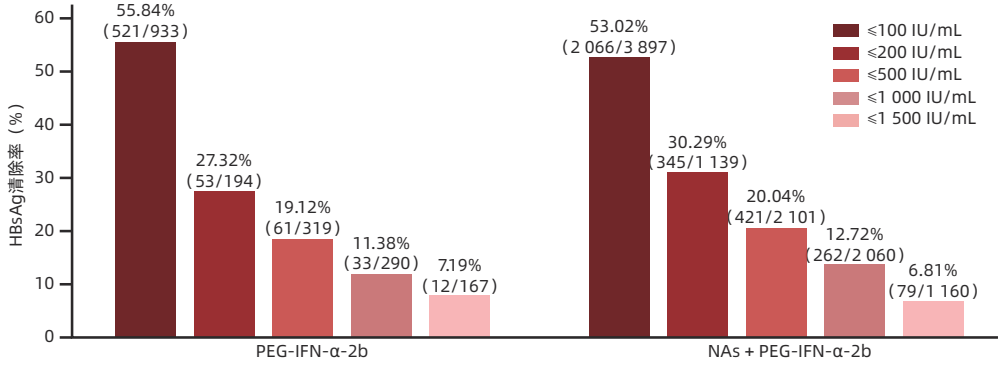

图2 对NAs治疗的CHB优势人群，加用或单用PEG-IFN-α的功能性治愈率

Figure 2 Functional cure rates of highly selected chronic hepatitis B patients treated with nucleos(t)ide analogues who receive an add-on or monotherapy of pegylated interferon-α

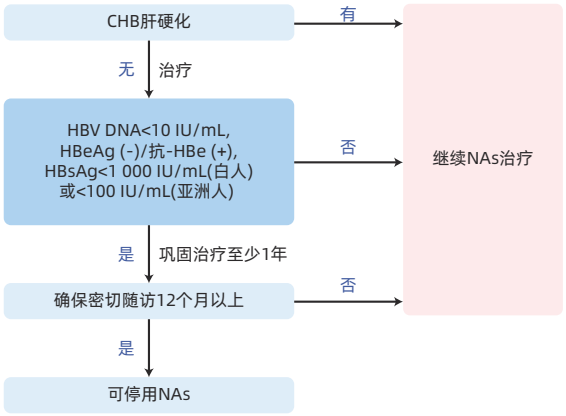

图3　CHB患者NAs有限疗程治疗策略

Figure 3　Finite treatment strategies of nucleos(t)ide analogues for chronic hepatitis B

2～3月检测1次ALT和HBV DNA，评价其是否需要再治疗。1年后每3～6个月监测1次[17]。

2　提高CHB功能性治愈率的新药

2.1　反义寡核苷酸Bepirovirsen（BPV）Ⅱb期临床试验　BPV Ⅱb期B-Clear多中心随机开放临床试验，将入组的CHB患者随机分为A、B、C、D 4组，A组每周皮下注射BPV 300 mg，连续治疗24周，该组进一步分为NAs治疗组（68例）和初治组（70例），停药时两组HBsAg消失率分别为26%和29%，停药后24周时，两组HBsAg消失率分别为12%和14%[21]。

BPV Ⅱb期B-Together多中心随机开放临床试验中，CHB患者每周皮下注射BPV 300 mg，连续治疗24周，之后每周皮下注射PEG-IFN-α 180 μg，治疗24周，PEG-IFN-α停药后随访24周，所有入组患者的HBsAg和HBV DNA消失率为9%（5/55），基线HBsAg≤3 000 IU/mL患者的HBsAg和HBV DNA消失率为14%（5/37）（图4）。上述结果提示，BPV与PEG-IFN-α序贯治疗可提高HBsAg和HBV DNA消失率[22]。BPV Ⅲ期临床试验（B-Well）正在进行中[23-24]。

2.2　siRNA Xalnesiran（RG6346）的Ⅱ期临床试验　罗氏公司研发的Xalnesiran联合PEG-IFN-α或Ruzotolimod（一种Toll样受体7激动剂）Ⅱ期临床试验的入组患者标准是：（1）CHB≥6个月；（2）NAs治疗≥12个月；（3）HBV DNA<定量下限（LLOQ）或<20 IU/mL；（4）ALT<1.5×ULN；（5）无肝硬化。将入组的CHB患者随机分为5组：A组30例，Xalnesiran（100 mg，每4周皮下注射）+NAs，治疗48周；B组30例，Xalnesiran（200 mg，每4周皮下注射）+NAs，治疗48周；C组34例，Xalnesiran（200 mg，每4周皮下注射）+NAs，治疗48周，另于第12～24周和第36～49周分别每日1次口服Ruzotolimod 150 mg；D组30例，Xalnesiran（200 mg，每4周皮下注射）+NAs+PEG-IFN-α（180 μg，每周皮下注射1次），治疗48周；E组36例，服用NAs作为对照组。但各组患者均持续服用NAs，直至符合停药标准。A、B、C、D和E组于停药后均随访24周，其HBsAg消失（<0.05 IU/mL）率分别为7%、3%、12%、23%和0%，提示Xalnesiran联合PEG-IFNα或Ruzotolimod可提高HBsAg消失率。但HBsAg消失只见于基线HBsAg<1 000 IU/mL的CHB患者[25-26]。

2.3　衣壳组装调节剂（capsid assembly modulator，CAM）+siRNA+NAs Ⅱb期临床试验（REEF-2）　CAM+siRNA+NAs Ⅱb期临床试验（REEF-2）为双盲、安慰剂对照随机研究，入组130例经NAs治疗HBV DNA完全抑制的HBeAg阴性CHB患者，试验组85例，接受JNJ-3989（siRNA，200 mg，每4周皮下注射1次）+JNJ-6379（CAM，250 mg，每日口服1次）+NAs（每日口服）；安慰剂组用JNJ-3989安慰剂+JNJ-6379安慰剂+NAs，两组均治疗48周，停药后随访48周。

随访至停药后24周和48周，无1例患者获得功能性治愈（HBsAg消失），但治疗至48周，试验组HBsAg平均下降水平较安慰剂组显著（1.89 $\log_{10}$ IU/mL vs 0.06 $\log_{10}$ IU/mL，P=0.001）；随访至48周时，试验组HBsAg水平较基线下

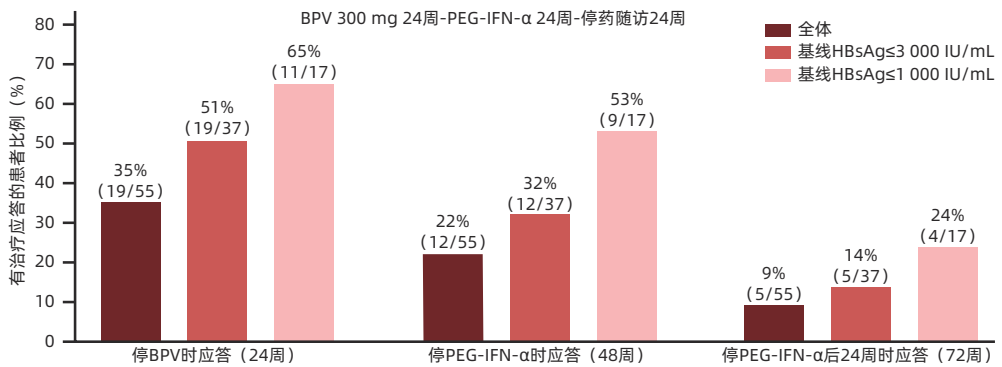

图4　BPV Ⅱb期B-Together临床试验

Figure 4　B-Together clinical trail of Bepirovirsen in phase Ⅱb

降>1 $\log_{10}$ IU/mL 占 81.5%，安慰剂组仅为 12.5%；试验组 HBsAg<100 IU/mL 患者占比大于安慰剂组（46.9% vs 15.0%）。停药后，试验组 HBV DNA 复阳和 ALT 升高率（再治疗率）低于安慰剂组（9.1% vs 26.8%）。上述结果提示，CAM+siRNA+NAs 联合治疗可明显降低 HBsAg 水平，但无 1 例获得功能性治愈[27]。

2.4 Ⅱ期临床试验在研免疫调节剂新药 目前有多种 CHB 免疫调节剂进入Ⅱ期临床试验（表 1），但至今尚无一种被证明可获得功能性治愈[28]。

3 联合治疗

其他感染性疾病如艾滋病和丙型肝炎药物联合治疗的成功经验表明，慢性 HBV 感染要达到功能性治愈也需要联合治疗。虽然目前已有 NAs 和 PEG-IFN-α 抗 HBV 药物，并有 40 余种新药正在研发中，但功能性治愈方案主要还是凭临床实践经验，缺乏对控制 HBV 复制和 HBsAg 消失机制的深入认识。目前功能性治愈最有希望的治疗策略是抑制病毒复制、降低 HBV 抗原产生、恢复对 HBV 的免疫应答（图 5）[28]。

目前，联合治疗的研究焦点是何时联合、不同药物如何序贯治疗及其治疗的持续时间等。此外，可能还需要考虑如何基于 CHB 患者基线 HBeAg 状况、HBV DNA 载量、HBsAg 水平，以及有无肝硬化等因素，制订个体化的治疗方案。

道长且阻，行则将至！CHB 功能性治愈不是梦，人类终将完全治愈 HBV 感染！

利益冲突声明：本文不存在任何利益冲突。

表 1 进入Ⅱ期临床试验的免疫调节剂新药[28]

Table 1 Novel immunomodulators for hepatitis B treatment in phase Ⅱ clinical trails

药物	药名	用药途径和剂量	临床试验
诱导固有免疫			
Toll 样受体 7 拮抗剂	R07020531	口服，150 mg/d	Ⅱ期
Toll 样受体 8 拮抗剂	Selgantolimod	口服，1.5～3.0 mg/周	Ⅱ期
诱导适应性免疫			
可溶性双特异性 T 淋巴细胞受体	IMC-1109V		Ⅰ期
检查点抑制剂	ASC22	皮下注射，0.3～2.5 mg/kg	Ⅱ期
治疗性疫苗	BRII 179（VBI-2501）	肌内注射	Ⅱ期
	HepTcell	肌内注射	Ⅱ期
	GSK3528869A	肌内注射	Ⅰ/Ⅱ期
	VVX001	皮下注射	Ⅱ期
	VTP-300	肌内注射	Ⅱ期

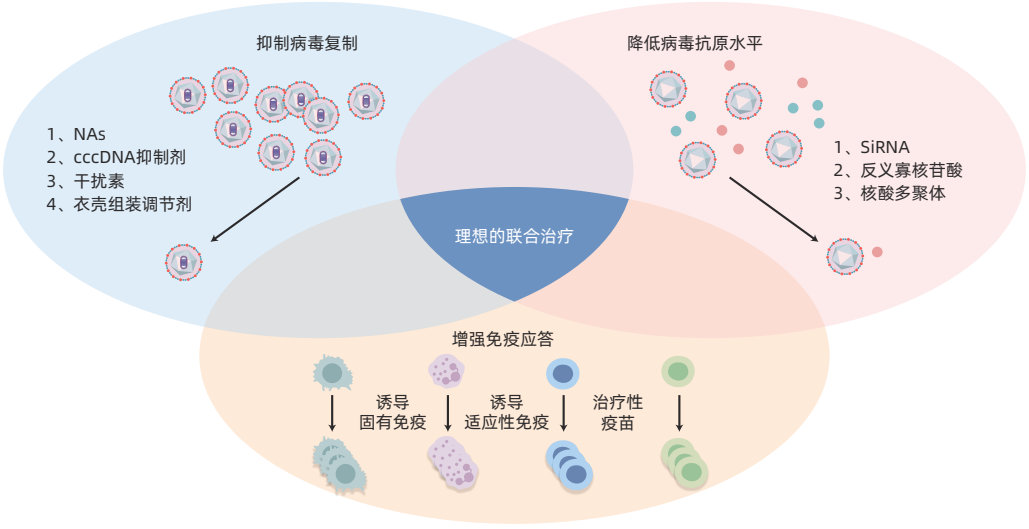

图 5 CHB 理想的联合治疗策略

Figure 5 Ideal combination treatment strategies for functional cure of chronic hepatitis B

参考文献：

[1] CHAI N, CHANG HE, NICOLAS E, et al. Properties of subviral particles of hepatitis B virus[J]. J Virol, 2008, 82(16): 7812-7817. DOI: 10.1128/JVI.00561-08.

[2] GANEM D, PRINCE AM. Hepatitis B virus infection: Natural history and clinical consequences[J]. N Engl J Med, 2004, 350(11): 1118-1129. DOI: 10.1056/NEJMra031087.

[3] REHERMANN B, LAU D, HOOFNAGLE JH, et al. Cytotoxic T lymphocyte responsiveness after resolution of chronic hepatitis B virus infection[J]. J Clin Invest, 1996, 97(7): 1655-1665. DOI: 10.1172/JCI118592.

[4] BONI C, LACCABUE D, LAMPERTICO P, et al. Restored function of HBV-specific T cells after long-term effective therapy with nucleos(t)ide analogues[J]. Gastroenterology, 2012, 143(4): 963-973. DOI: 10.1053/j.gastro.2012.07.014.

[5] KIM JH, GHOSH A, AYITHAN N, et al. Circulating serum HBsAg level is a biomarker for HBV-specific T and B cell responses in chronic hepatitis B patients[J]. Sci Rep, 2020, 10(1): 1835. DOI: 10.1038/s41598-020-58870-2.

[6] RINKER F, ZIMMER CL, HÖNER ZU SIEDERDISSEN C, et al. Hepatitis B virus-specific T cell responses after stopping nucleos(t)ide analogue therapy in HBeAg-negative chronic hepatitis B[J]. J Hepatol, 2018, 69(3): 584-593. DOI: 10.1016/j.jhep.2018.05.004.

[7] van BÖMMEL F, BERG T. Risks and benefits of discontinuation of nucleos(t)ide analogue treatment: A treatment concept for patients with HBeAg-negative chronic hepatitis B[J]. Hepatol Commun, 2021, 5(10): 1632-1648. DOI: 10.1002/hep4.1708.

[8] LOK ASF. Toward a functional cure for hepatitis B[J]. Gut Liver, 2024, 18(4): 593-601. DOI: 10.5009/gnl240023.

[9] GHANY MG, BUTI M, LAMPERTICO P, et al. Guidance on treatment endpoints and study design for clinical trials aiming to achieve cure in chronic hepatitis B and D: Report from the 2022 AASLD-EASL HBV-HDV treatment endpoints conference[J]. J Hepatol, 2023, 79(5): 1254-1269. DOI: 10.1016/j.jhep.2023.06.002.

[10] LI MH, YI W, ZHANG L, et al. Predictors of sustained functional cure in hepatitis B envelope antigen-negative patients achieving hepatitis B surface antigen seroclearance with interferon-alpha-based therapy[J]. J Viral Hepat, 2019, 26(Suppl 1): 32-41. DOI: 10.1111/jvh.13151.

[11] LI MH, SUN FF, BI XY, et al. Consolidation treatment needed for sustained HBsAg-negative response induced by interferon-alpha in HBeAg positive chronic hepatitis B patients[J]. Virol Sin, 2022, 37(3): 390-397. DOI: 10.1016/j.virs.2022.03.001.

[12] YIP TCF, WONG GLH, WONG VWS, et al. Durability of hepatitis B surface antigen seroclearance in untreated and nucleos(t)ide analogue-treated patients[J]. J Hepatol, 2018, 68(1): 63-72. DOI: 10.1016/j.jhep.2017.09.018.

[13] LOK AS, ZOULIM F, DUSHEIKO G, et al. Durability of hepatitis B surface antigen loss with nucleotide analogue and peginterferon therapy in patients with chronic hepatitis B[J]. Hepatol Commun, 2019, 4(1): 8-20. DOI: 10.1002/hep4.1436.

[14] YIP TCF, LOK ASF. How do we determine whether a functional cure for HBV infection has been achieved?[J]. Clin Gastroenterol Hepatol, 2020, 18(3): 548-550. DOI: 10.1016/j.cgh.2019.08.033.

[15] XIE C, LIN BL, XIE DY, et al. Peginterferon alpha-2b promoted HBsAg loss in nucleos(t)ide analogue-treated patients: a large-scale real-world study (Everest Project)[J]. J Hepatol, 2026 (Revised).

[16] GAO N, GUAN GW, XU GL, et al. Integrated HBV DNA and cccDNA maintain transcriptional activity in intrahepatic HBsAg-positive patients with functional cure following PEG-IFN-based therapy[J]. Aliment Pharmacol Ther, 2023, 58(10): 1086-1098. DOI: 10.1111/apt.17670.

[17] HIRODE G, CHOI HSJ, CHEN CH, et al. Off-therapy response after nucleos(t)ide analogue withdrawal in patients with chronic hepatitis B: An international, multicenter, multiethnic cohort (RETRACT-B study)[J]. Gastroenterology, 2022, 162(3): 757-771. DOI: 10.1053/j.gastro.2021.11.002.

[18] LIM SG, TEO AE, CHAN ESY, et al. Stopping nucleos(t)ide analogues in chronic hepatitis B using HBsAg thresholds: A meta-analysis and meta-regression[J]. Clin Gastroenterol Hepatol, 2024. DOI: 10.1016/j.cgh.2024.05.040. [Online ahead of print]

[19] BLOCK PD, LIM JK. Unmet needs in the clinical management of chronic hepatitis B infection[J]. J Formos Med Assoc, 2024. DOI: 10.1016/j.jfma.2024.08.020. [Online ahead of print]

[20] PETERS MG, YUEN MF, TERRAULT N, et al. Chronic hepatitis B finite treatment: Similar and different concerns with new drug classes[J]. Clin Infect Dis, 2024, 78(4): 983-990. DOI: 10.1093/cid/ciad506.

[21] YUEN MF, LIM SG, PLESNIAK R, et al. Efficacy and safety of Bepirovirsen in chronic hepatitis B infection[J]. N Engl J Med, 2022, 387(21): 1957-1968. DOI: 10.1056/NEJMoa2210027.

[22] BUTI M, HEO J, TANAKA Y, et al. Sequential Peg-IFN after bepirovirsen may reduce post-treatment relapse in chronic hepatitis B[J]. J Hepatol, 2024. DOI: 10.1016/j.jhep.2024.08.010. [Online ahead of print]

[23] Study of Bepirovirsen in nucleos(t)ide analogue-treated participants with chronic hepatitis B (B-Well 1)[R/OL]. [2024-11-16]. http://ClinicalTrials.gov identifier NCT05630807.

[24] Study of Bepirovirsen in nucleos(t)ide analogue-treated participants with chronic hepatitis B (B-Well 2)[R/OL]. [2024-11-16]. http://ClinicalTrials.gov identifier NCT05630820.

[25] HOU JL, XIE Q, ZHANG WH, et al. OS-030 efficacy and safety of xalnesiran with and without an immunomodulator in virologically suppressed participants with chronic hepatitis B: end of study results from the phase 2, randomized, controlled, adaptive, open-label platform study (PIRANGA)[J]. J Hepatol, 2024, 80: S26. DOI: 10.1016/S0168-8278(24)00471-9.

[26] HOU JL, ZHANG WH, XIE Q, et al. Xalnesiran with or without an immunodulator in chronic hepatitis B[J]. N Engl J Med, 2024, 391(22): 2098-2109. DOI: 10.1056/NEJMoa2405485.

[27] AGARWAL K, BUTI M, van BÖMMEL F, et al. JNJ-73763989 and bersacapavir treatment in nucleos(t)ide analogue-suppressed patients with chronic hepatitis B: REEF-2[J]. J Hepatol, 2024, 81(3): 404-414. DOI: 10.1016/j.jhep.2024.03.046.

[28] GOPALAKRISHNA H, GHANY MG. Perspective on emerging therapies to achieve functional cure of chronic hepatitis B[J]. Curr Hepatol Rep, 2024, 23(2): 241-252. DOI: 10.1007/s11901-024-00652-9.

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