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Two types of viral hepatitis, two different treats from pharma- what's after the liver meeting® 2014?

Abstract

During recent years, huge progress has been made toward developing directing-acting antivirals (DAAs) for the treatment of chronic hepatitis C (CHC). Clinical data announcement from ongoing CHC trials has become the center piece of the annual Liver Meeting. As DAA combinations are approaching 95-100% efficacy with great tolerability, there is limited room for developing better therapeutics. Scientific and medical communities as well as drug companies are turning their attention to other liver diseases. One of the renewed interesting areas is chronic hepatitis B (CHB), a disease that affects more people world-wide than CHC does. Although pegylated interferon may lead to functional cure of CHB in some patients, the effect is still very modest. New HBV drugs with novel mode of actions are entering into clinical development with the aim to maximize functional cure of CHB. Finally, there are other liver diseases, such as nonalcoholic steato hepatitis (NASH) and hepatocellular carcinoma (HCC) that are also drawing research and development interest.

Keywords: Directing-acting antivirals, Chronic hepatitis C, Chronic hepatitis B, Functional cure, Nonalcoholic steato hepatitis, Hepatocellular carcinoma, HCV, HBV, HCC, CHB, CHC

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Yonghong Zhu
Department of Pharmacogenomics, Takeda Pharmaceuticals International, USA

Correspondence: Yonghong Zhu, Department of Pharmacogenomics, Takeda Pharmaceutical International, Inc, 1 Takeda Parkway, Tel 224-554-2800, Fax 224-554-1019; Email Yonghong.zhu@takeda.com

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Abbreviations: HCV, Hepatitis C Virus; CHC, Chronic Hepatitis C; NS5, Non-Structural Protein 5; RBV, Ribavirin; SOC, Standard of Care; GT, Genotype; AASLD, American Association for the Study of Liver Diseases; IDSA, Infectious Diseases Society of American; sNDA, supplemental New Drug Application; IAS-USA, International Antiviral Society-USA

History of HCV discovery and treatment of chronic HCV infection

In 1989, scientists at Chiron (acquired by Novartis in 2006), in collaboration with a CDC researcher, first reported the molecular cloning of hepatitis C virus (HCV) genome from serum samples of patients diagnosed with Non-A Non-B viral hepatitis.[1] After the discovery of HCV, tremendous progress has been made toward better understanding the virus itself and its associated chronic hepatitis C (CHC). CHC affects approximately 130-150 million people globally and leads to 350,000-500,000 death annually.[2] Based on phylogenetic analysis of nucleotide sequences at either non-structural protein 5 (NS5) region or 5" untranslated region of HCV genome, HCV are classified into 6 genotypes (GT1-6). Variations at NS5 region can also divide genotype 1 into 1a and 1b sub genotypes [3]. In the same year of the discovery of HCV, recombinant interferon Alfa (IFN) showed effective in treating CHC.[4] Since then, the treatment paradigm has shifted from recombinant interferon Alfa to peginterferon Alfa-2 (pegIFN) and was quickly followed by the regimen of IFN in combination with Ribavirin (RBV).[5] From 2001 to 2011, pegIFN plus RBV was the standard-of-care (SOC) that cured about 40-51% of HCV genotype 1 (GT1) and 70-75% of genotype 2-6 (GT2-6) virus infection in treatment-naive patients in global Phase 3 trials.[6-9] Of particular note, patients with HCV genotype 5 and 6 were recruited into pegIFN/RBV registration trials. However, the number was too low to make a dose recommendation in the prescribing information (Table 1).[8,9]

During the heydays of pegIFN/RBV as SOC, tremendous efforts and progresses have been made toward developing antiviral agents with better efficacy, tolerability, shorter duration, as well as for patients with unmet medical needs such as SOC non responders, intolerant/ineligible patients. This mini review is aimed at summarizing what have been made in the rapid progress of drug development in CHC at the time of the Liver Meeting 2014 and what is beyond CHC for another viral hepatitis, chronic hepatitis B (CHB) from drug development prospective.

Post Pegifn/Rbv Era: The Short Life of Direct-Acting Antiviral (Daa) + Pegifn/Rbv Triple Regimen

In 2011, two direct-acting antivirals (DAAs) that target HCV NS3/4A protease, telaprevir (Incevik, Vertex) and boceprevir (Victrelis, Merck) were separately approved in combination with pegIFN/RBV which achieves 63% and 79% sustained virologic response at 24-wk after the end of treatment (SVR24) in GT1 virus infected, treatment-naïve patients in global phase 3 trials.[10,11] These two triple regimens brought efficacy to a new level but both regimens have their limitations such as side effects and complicated treatment algorithms (Table 1). Perceived as modestly better on the efficacy side, Incevik even reached blockbuster drug status in US with 1.16 billion USD sale during the first full launch year of 2012.[12] However, in 2013, this drug only generated 446 million USD annual sales [13]. Fast forward to the first 3 quarters of 2014, the sale number was only 23.5 million USD in US.[14] This drastic decline in prescription reflected the fact that Incevik was no match for the efficacy and tolerability against the 2nd generation of DAAs, which was on the horizon. Both patients and doctors would rather wait for the new treatment unless immediate care was needed. On Aug 11th, 2014 Vertex wrote to the healthcare providers that it would stop the sale of Incevik in USA.

In late 2013, 2 additional DAAs, Simprevir (Olysio, Johnson) and Sofospuvir (Sovaldi, Gilead) were approved by FDA in combination with pegIFN/RBV. While Olysio is a potent HCV genotype 1 (GT1) NS3/4A protease inhibitor, Sovaldi is a unique pan-genotypic NS5B nucleotide polymerase inhibitor that has a high genetic barrier for viral resistance. Both regimens in clinical studies demonstrated impressive

sustained virologic response at 12-wk after the end of treatment (SVR12) of >80-90% in treatment-naive, GT1 HCV-infected patients.[15,16] Furthermore, Sovaldi plus RBV was also licensed as the 1st all oral, interferon-free regimen not only for HCV GT2/3 infection but also for treating interferon-ineligible, HCV GT1-infected patients. It's not surprising to see that, since the launch of Sovaldi (approved in Dec 2013), in 2014 the 1st 3 quarter sales of the drug reached 2.3, 3.5, and 2.8 billion USD respectively.[17,18] making it the fastest drug to reach blockbuster sales status and potentially challenge adalimumab (Humira, Abbvie) as the top-selling medicine in 2014. As the runner-up, the use of Olysio was also well accepted. During 2014 the 1st 3 quarter sales of the drug reached 354 million, 831 million, and 796 million separately.[19,20] Ironically, the use of Olysio was predominantly prescribed together with Sovaldi. However, this off-label use of Olysio and Sovaldi was soundly built on the strong scientific rationale from the results of Phase 2 COSMOS study. In this study, the combined use of Olysio and Sovaldi cured >90% of GT1-infected, treatment-naïve or prior null responders, with or without advanced fibrosis.[21] In addition, the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of American (IDSA) in collaboration with International Antiviral Society-USA (IAS-USA) had also recommended the off-label use of Sovaldi plus Olysio for certain HCV patient populations. Janssen submitted a supplemental New Drug Application (sNDA) to the FDA based on the results from COSMOS study.

Table 1 pegIFN based regimens on market

Treatment	Approval year	Total treatment duration (Treatment-naive or prior relapser)	Total treatment duration (GT1 Partial or null responders to P/R)
pegIFN/RBV (P/R)	2001 (Pegintron) 2002 (Pegasys)	GT1/4: 48 wk GT2/3: 24 wk GT5/6: 48 wk (per clinical practice)(56)	
pegIFN/RBV+Victrelis (P/R/V)	2011	GT1 (RGT eligible): 4-wk P/R+24-wk P/R/V GT1 (RGT ineligible): 4-wk P/R+32-wk P/R/V+12-wk P/R GT1 with cirrhosis: 48 wk GT1 relapsers (RGT eligible): 4-wk P/R+32-wk P/R/V GT1 relapsers (RGT ineligible): 4-wk P/R+32-wk P/R/V+12-wk P/R	Partial responders (RGT eligible): 4-wk P/R+32-wk P/R/V Partial/relapsers (RGT ineligible): 4-wk P/R+32-wk P/R/V+12-wk P/R Null responders: 4-wk P/R+44-wk P/R/V
pegIFN/RBV+Incevik (P/R/I)	2011	GT1 naïve or relapsers (RGT eligible): 12-wk P/R/I+12-wk P/R GT1 naïve or relapsers (RGT ineligible): 12-wk P/R/I+36-wk P/R	12-wk P/R/I+36-wk P/R
pegIFN/RBV+Olysio (P/R/O)	2013	GT1: 12-wk P/R/O+12-wk P/R	12-wk P/R/O+36 P/R
pegIFN/RBV+Sovaldi (P/R/S)	2013	GT1/4: 12-wk GT3: 12-wk (EU only) GT5/6: 12-wk (EU only)	
pegIFN/RBV+Daklinza (P/R/D)	2014 (EU only)	GT4: 24 wk or 48 wk	

PegIFN: Peginterferon Alfa-2; RBV: Ribavirin; GT: Genotype; RGT: Response Guided Treatment; EU: European Union

New Era of Ifn-Free Daa Combo Regimen

After the initial triumph of interferon-free regimens (licensed or off-label), several key regulatory milestones of DAA combo regimens were achieved: On July 7th, 2014, Bristol Meyer Squibb announced that Japan has become the first country to approve 2 novel DAA-based combo regimen of Daklinza (daclatasvir), a pan-genotypic NS5A replication complex inhibitor, and Sunvepra (asunaprevir), a GT1 NS3/4A protease inhibitor.[22] This regimen was approved for chronic HCV GT1b-infected patients who are either interferon ineligible/intolerant to or have failed interferon-based therapy. GT1b is the dominant HCV sub-genotype in Japan. Phase 3 study in Japan (NCT01497834) demonstrated an overall response rate of 85% (87.4% in interferon ineligible/intolerant and 80.5% IFN null/partial responders).[23] The response rate in Japanese HCV population appears very similar to a global Phase 3 trial (HALLMARK-DUAL) in which the races of White, Black, and Asian were all recruited. In this study, the combo treatment cured 90% of treatment-naive, 82% of IFN-treatment failure, and 82% of interferon-ineligible/intolerant patients.[24]

One month after the approval of Daklinza approval in Japan, the European Commission approved Daklinza for use in combination with either Sovaldi (with or without Ribavirin) or pegIFN/RBV for the treatment of chronic HCV GT1-4 infection in adults.[25] In an open label Phase 2 study (AI444040), Daklinza/Sovaldi combo cured 99% of treatment-naïve HCV GT1 infection, 100% of GT1 infection that either Incevik or Victrelis failed to clear, 92% of GT2 and 89% of GT3 infection.[26] The GT3 data was further backed up by an additional Phase 3 ALLY-3 study which showed that 12-wk combo treatment achieved 90% SVR12 for treatment-naïve and 86% SVR12 for treatment-experienced GT3 patients.[27] For GT2 infection, even though the 24-wk combo (+/-RBV) regimen was effective in curing 96% of patients, it was not the recommended regimen for treating patients as Sovaldi plus RBV for 12-wk was sufficient for curing 95% of treatment-naive patients and 93% of interferon-

intolerant/ineligible/unwilling GT2 patients (Data from Gilead Fission and Positron studies described in Sovaldi label).[28] Of particular interest, Daklinza + Sovaldi combo was also recommended for treating GT4 infection as an oral regimen in addition to the approved Daklinza plus pegIFN/RBV treatment.[25]

In Oct 2014, FDA approved Harvoni (a fixed dose combination of sofosbuvir and ledipasvir, a NS5A inhibitor) for treating GT1 infection with 8-wk, 12-wk, 24-wk treatment durations based on prior treatment history, baseline viral load, and cirrhotic status with ≥ 94% SVR12 in three Phase 3 trials.[28] Additionally, in Nov 2014, FDA also approved Olysio and Sovaldi combo for treating GT1 infection with 12- or 24-wk treatment pending on cirrhosis status. As mentioned

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previously, the sNDA approval was again based on COSMOS trial. For all patients in the COSMOS trial (treatment-naive and treatment-experienced, METAVIR F0-F4), 93 percent achieved SVR12 after 12 weeks and 97% achieved SVR12 after 24 weeks of treatment.[21]

Table 2 IFN-free regimens on market

DAA combo	Approval year	Duration for treatment-naïve patient and SVR rate	Prior partial or null responders to P/R and SVR rate
Sovaldi+ RBV	2013	GT2: 12 wk, 95-97% GT3: 24 wk, 93% GT1/4/5/6 IFN ineligible: 24-wk (4/5/6 EU only), 65% (only GT1 Ph2 data)	GT2: 12-wk, 82-90% (including relapsers) GT3: 24-wk, 77% (including relapsers)
Daklinza+ Sunvepra	2014 (Japan only)	GT1b : 24-wk (IFN ineligible / intolerant only), 87.4% (Japan Ph3), 82% (Hallmark-Dual)	GT1b: 24-wk, 80.5% (Japan Ph3), 82% (Hallmark-Dual)
Olysio+ Sovaldi	2014	GT1: 12 wk, 95% GT1 with cirrhosis: 24-wk, 100%	GT1: 12 wk, 95% GT1 with cirrhosis: 24-wk, 100%
Harvoni (ledipasvir+sofosbuvir)	2014	GT1: 12 wk, 96-99% GT1 IL28B CC: 8-wk (EU only) GT4 (EU): 12-wk (EU only) GT1/4 cirrhosis: 24 wk (EU only), 97% (GT1 data)	GT1: 12-wk, 95% GT1 with cirrhosis: 24 wk, 100%
Harvoni (ledipasvir+ sofosbuvir)+RBV	2014 (EU only)	GT3 cirrhosis: 24-wk	GT3: 24-wk
Daklinza+ Sovaldi	2014 (EU only)	GT1/4 no cirrhosis: 12 wk, 100% (GT1 data) GT1/4 cirrhosis: 24 wk, 100% (GT1 data) GT1 cirrhosis cc: 12 wk, 100%	
Daklinza+ Sovaldi+ RBV	2014 (EU only)	GT3 cirrhosis: 24 wk, 100%	GT3: 24-wk

DAA: Direct-Acting Antiviral Agents; SVR: Sustained Virologic Response; PegIFN: Peginterferon Alfa-2; R: Ribavirin; RBV: Ribavirin; GT: Genotype; RGT: Response Guided Treatment; EU: European Union

Starting from Sovaldi/Ribavirin, followed by Daklinza/Sunvepra, Olysio/Sovaldi, Harvoni (Sofospuvir and ledipasvir), Daklinza/Sovaldi, this wave of IFN-free regimens brought SVR to the new standard of >80-90% in GT1 infection (Table 2). While these combo regimens are potent, they do have their niche. Sovaldi/Ribavirin takes care of GT2 and 3 but its efficacy appears modest in GT1 IFN-ineligible patients and GT2 and 3 treatment failures. Daklinza/Sunvepra combo only works well in GT1b patients due to the limitation of Sunvepra. Olysio/Sovaldi, Harvoni, and Daklinza/Sovaldi work equally well against GT1 infection. Harvoni and Daklinza/Sovaldi can also be used for treating GT4 and GT3 infection. Nevertheless, RBV is still needed for treating GT3 infection with Harvoni and Daklinza/Sovaldi. These combos (except Sovaldi/Ribavirin) are based on different mode of action, thus further reducing the risk of resistance development. Even though Daklinza and Sovaldi are pan-genotypic and show good promise, maximizing its utility seems limited due to the fact that Gilead is more interested in developing fixed dose combination of Sovaldi with its other anti-HCV molecules.

DAA Combos Waiting For Regulatory Approval and in Development

Coming next, the lists of combination therapeutics waiting for regulatory approval are Abbevie's 3D regimen and BMS's Trio regimen, both of which are for GT1 infection (Table 2). Abbvie's 3D regimen is a cocktail which contains Ritonavir-boosted NS3/4A protease inhibitor ABT-450 co-formulated with NS5A inhibitor ombitasvir (ABT-267), as well as the non-nucleoside polymerase inhibitor dasabuvir (ABT-333). To support its regulatory filing(Approved by FDA on December 19, 2014 as VIEKIRA PAK™), Abbvie conducted 6 Phase 3 studies in GT1 patients. With RBV, SVR12 of 12-wk 3D regimen was 91.8% and SVR12 of 24-wk treatment reached 96.5% in cirrhotic, treatment-naive or -experienced patients (TURQUOISE-II study).[29] With RBV, SVR12 of 12-wk treatment was 96.2% in non-cirrhotic, treatment-naive patients (Sapphire-I study, NCT01716585).[30] With RBV, SVR12 of 12-wk treatment was 96.3% in non-cirrhotic, treatment-experienced patients (Sapphire-II study, NCT01715415).[31] In PEAR-II study (NCT01674725) of GT1b treatment-experienced patients, SVR12 for 12-wk Trio treatment was 97% (+RBV) and 100% (-RBV).[32] In Pear-III study (NCT01767116) of treatment-naïve GT1b patients, 12-wk regimen achieved SVR12 of 99.5% (+RBV) and 99% (-RBV). In Pearl-IV study (NCT01833533) of treatment-naive GT1a patients, 12-wk regimen achieved SVR12 of 97% (+RBV) and 90.2% (-RBV).[33] Finally, even in HCV GT1/HIV co-infected patients, the 3D regimen with RBV achieved SVR of 93.5% by 12-wk treatment and SVR of 90.6% by 24-wk treatment (TURQUOISE-I Ph2/3 study, NCT01939197).[34]

BMS's Trio regimen is a fixed-dose combination of NS5A inhibitor daclatasvir, NS5A protease inhibitor asunaprevir, and non-nucleoside polymerase inhibitor beclabuvir. Phase 3 UNITY-1 study (-RBV) evaluated a 12-week regimen of the TRIO regimen in treatment-naive and -experienced non-cirrhotic patients. Overall 91% of patients achieved SVR12 (92% SVR12 in treatment-naive patients and 89% SVR12 in treatment-experienced patients).[35] Phase 3 UNITY-2 study evaluated in cirrhotic, treatment-naive and- experienced patients. 12-wk Trio regimen (+RBV) led to 96% SVR12 (98% SVR12 in treatment-naïve and 93% SVR12 in treatment-experienced patients) while 12-week Trio regimen (-RBV) achieved overall 90% SVR12 (93% SVR12 in treatment-naive and 87% SVR12 in treatment-experienced patients).[36]

Overall, these two combo regimens covers GT1 very well and can become strong challengers against Harvoni by Gilead. However, there is still room for improvement as adding RBV as well as 24-week treatment duration are still needed to maximize the efficacy in GT1 cirrhotic patients, especially in GT1a subgeotype. So far, these newly approved and emerging combo regimens have significantly raised the bar for future DAA combo development to regimens of >95% SVR12 and <12-wk therapy and ideally with pan-genotypic coverage and no RBV. As front runners are building the lead, the fast followers are also doing risk-taking, innovative approach to develop new treatment paradigm (Table 3). An example is in an ongoing Phase 2 study, Merck included a 4-week combo treatment of grazoprevir (MK5172,

a protease inhibitor)/elbasvir (MK-8742, a NS5A inhibitor) plus Sovaldi in GT1 treatment-naive patients. Unfortunately, 61.3% of patients relapsed prior to post dosing 12-week.[37] Another example is that Achillion conducted a Phase 2a study of 6-wk or 8-wk combo treatment of ACH-3102 (a NS5A inhibitor) plus Sovaldi in treatment-naive, GT1 patients. Of the 12 treated patients, 100% achieved SVR12.[38] Furthermore, due to the fierce competition, it's also within expectation that there will be players exiting from the field and players making additional acquisitions to strengthen their presence. Similar to Vertex, Boehringer Ingelheim has bowed out of the race and withdrawn all regulatory filings for faldaprevir, a mediocre NS3/4A protease inhibitor. They also abandoned the development of oral DAA combo of faldaprevir, deleobuvir (non-nucleoside NS5B polymerase inhibitor) and Presidio's PPI-668 (NS5A inhibitor). BMS also withdrew NDA of daclatasvir and asunaprevir combo from FDA for HCV GT 1b indication. On the other hand, several pharmaceutical companies have been attempting to enhance their pipeline in order to compete at the next level. As a matter of fact, Merck bought Idenix for 3.85 billion in June 2014 to gain access to its 2 nucleotide analogues: IDX21437 and IDX21459 as well as samatasvir (NS5A inhibitor) to expand its pipeline beyond grazoprevir and elbasvir. In Sept 2014, Janssen bought Alios with a 1.75 billion price tag for their nucleotide NS5B inhibitors of AL-335, AL-516, and potentially ALS-2200 (VX-135). PPI-668 from Presidio was subsequently licensed to Egypt-based Pharco Pharmaceuticals for treating HCV infection in Egypt as well as to China-based biotech firm Ascletis for clinical development within China. As Ascletis is also developing NS3/4A protease inhibitor danoprevir (ASC-08, partnering with Roche) in China, it's expected that Ascletis could develop an oral combo based on ASC-16 (PPI-668) and ASC-08 (danoprevir) (Table 3).

In parallel with the high efficacy, the new DAA regimen does not come out cheap. A 12-wk course of Sovaldi costs 84,000 USD. Additionally, a 12-week course of Olysio costs 66000 USD. Furthermore, a 12- week course of Harvoni is 94500 USD. Theoretically these DAA regimens might eventually eliminate HCV infection. However, the striking barrier to achieving this goal will be hinged on how to afford these wonder drugs. In many developing countries where HCV is endemic, interferon-based therapy will likely remains the first choice simply due to economical reasons. If these new DAAs would ever be accessible in these countries, discounting prices should be considered. In Sept 2014, Gilead signed non-exclusive licensing agreements with seven India-based generic pharmaceutical companies to expand access to its chronic hepatitis C medicines in developing countries. In Oct 2014, BMS also announced that it will help 90 developing countries to gain access to daclatasvir by utilizing tiered pricing model, licensing agreement and working in collaboration with partners with the lowest tiered price tailored to low-income and least developed countries.

Current Status of CHB Treatment

While huge progress has been made in developing DAAs for the treatment of CHC, drug development against hepatitis B virus (HBV) has been relatively stagnant. Chronic hepatitis B (CHB) affects about 240 million people world-wide and more than 780 000 people die every year due to the consequences of hepatitis B.[39] Unlike HCV, there is highly effective vaccine against new HBV infection. As for treating CHB, there are 5 available nucleos (t) ide analogs (NUCs) of lamivudine, adefovir, telbivudine, entecavir and tenofovir plus one immune modulator, peginterferon Alfa-2a (pegIFN2a). Unfortunately, NUCs only block reverse transcription of HBV pregenomic RNA, resulting to the decline of HBV DNA but have no direct effect on the existing covalently closed circular DNA (cccDNA) minichromosome. As cccDNA is the template for viral transcription, NUCs are ineffective in suppressing the production and release of viral proteins including HBeAg and HBsAg, which trigger immune tolerance. Therefore, treating CHB with NUC is analogous to treating HIV infection with highly active antiretroviral therapy that has no effect on the integrated provirus of HIV. Rarely, finite-duration treatment with NUC is achievable for HBeAg-positive patients if they develop HBeAg seroconversion on treatment. However, duration is extremely unpredictable prior to therapy as it depends on when HBeAg seroconversion occurs. Thus NUC treatment generally has to be a life-long treatment for patients who cannot achieve a sustained virological response off-treatment, i.e. for HBeAg-positive patients without HBeAg seroconversion and in HBeAg-negative patients. On the contrary, a defined course of pegIFN2a treatment (i.e. 48-wk) may lead to immune control of HBV infection with an opportunity to obtain a sustained virological response off-treatment and a chance of HBsAg loss in patients who achieve and maintain undetectable HBV DNA.[9] Many clinical studies have demonstrated that in some patients, pegIFN2a can trigger functional cure of HBV infection, defined as an immune clearance status with HBsAg-negative serum with or without HBs seroconversion. In recent years, there were more new studies adopting different combination strategies of pegIFN2a and NUC. These strategies aimed at maximally disrupting immune tolerance and recovering viral antigen-specific immune response. So far the best results came from a 96-week, extended treatment of 47 HBeAg-positive CHB patients with pegIFN2a plus adefovir or lamivudine. The treatment led to HBeAg seroconversion rate of 46.8% at 48 weeks, 74.5% at 96 weeks (end of treatment), and 72.3% at 120 weeks (24-wk post treatment). Meanwhile, HBsAg seroconversion rate was 6.4% at 48 weeks, 21.3% at 96 weeks (end of treatment), and 27.7% at 120 weeks (24-wk post treatment).[40]

Table 3 IFN-free regimens waiting for approval and representative combo regimens in development

DAA combo	Study name (Clinical phase)	HCV GT1 patient classification	Duration of treatment and SVR rate
Combo regimen for approval			
Abbvie 3D regimen*+RBV: paritaprevir/r/ombitasvir+dasabuvir+RBV	Turquoise-II (Ph3)	Cirrhotic, Rx-naive (41-43%) or P/R-experienced (57-59%)	12-wk: 91.8% (GT1a 88.6%, GT1b 98.5%) 24-wk: 96.5% (GT1a: 95%, GT1b 100%)
Abbvie 3D regimen+RBV: paritaprevir/r/ombitasvir+dasabuvir+RBV	Sapphire-I (Ph3)	Non-cirrhotic , Rx-naive	12-wk: 96.2% (GT1a 95.3%, GT1b 98%)
Abbvie 3D regimen+RBV: paritaprevir/r/ombitasvir+dasabuvir+RBV	Sapphire-II (Ph3)	Non-cirrhotic, P/R-experienced	12-wk: 96.3% (GT1a 96%, GT1b 96.7%)
Abbvie 3D regimen+/-RBV: paritaprevir/r/ombitasvir+dasabuvir+/-RBV	Pearl-II (Ph3)	GT-1b, P/R-experienced	12-wk (+RBV): 97% 12-wk (-RBV): 100%
Abbvie 3D regimen+/-RBV: paritaprevir/r/ombitasvir+dasabuvir+/-RBV	Pearl-III (Ph3)	GT-1b, Rx-naive	12-wk (+RBV): 99.5% 12-wk (-RBV): 99%

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Table Continued...

DAA combo	Study name (Clinical phase)	HCV GT1 patient classification	Duration of treatment and SVR rate
Abbvie 3D regimen+/-RBV: paritaprevir/r/ombitasvir+dasabuvir+/-RBV	Pearl-IV (Ph3)	GT-1a, Rx-naive	12-wk (+RBV): 97% 12-wk (-RBV): 90.2%
Abbvie 3D regimen+/-RBV: paritaprevir/r/ombitasvir+dasabuvir+/-RBV	Turquoise-I (Ph2/3)	GT1/HIV, Rx-naive (66.7%) or P/R-experienced (33.3%)	12-wk: 93.5% 24-wk: 90.6%
BMS Trio regimen: daclastavir+asunaprevir+beclabuvir	UNITY-1 (Ph3)	GT1 Rx-naive	12-week: 92% (Rx-naive), 89% (Rx-experienced)
BMS Trio regimen+/-RBV: daclastavir+asunaprevir+ beclabuvir+/-RBV	UNITY-2 (Ph3)	Cirrhotic, Rx-naive or Rx-experienced (P/R+/-DAA with different MOA or host targeted antivirals)	Rx-naïve: 12-wk (+RBV): 98% (GT1a 97%, GT1b 100%) 12-wk (-RBV): 93% (GT1a 90%, GT1b 100%) Rx-experienced: 12-wk (+RBV): 93% (GT1a 91%, GT1b 100%) 12-wk (-RBV): 87% (GT1a 86%, GT1b 90%)
Representative combo regimen in pipeline			
grazoprevir+ elbasvir+ Sovaldi	C-SWIFT (Ph2)	GT1 (GT3 recruited but not reported), Rx-naïve +/-cirrhosis	4-wk: 38.7% (noncirrhosis, SVR4/8) 6-wk: 86.7% (noncirrhotic, SVR4/8) 6-wk: 80% (cirrhotic, SVR4/8) 8-wk: 94.7% (cirrhotic, SVR4/8)
ACH-3102+Sovaldi	Proxy (Ph2a)	GT1 Rx-naive	8-wk: 100% (N=12)
ASC-08(danoprevir)+ ASC-16(PPI-668)+/-RBV?	China market (Ph2)	GT1 in China	??

*Approved by FDA on December 19, 2014 as VIEKIRA PAK™

DAA: Direct-Acting Antiviral Agents; GT: Genotype; SVR: Sustained Virologic Response; r: Ritonavir; RBV: Ribavirin; Rx: Treatment; P: Peginterferon Alfa-2; R: Ribavirin; RGT: Response Guided Treatment; MOA: Mode of Action

Developing New Medicines for CHB

Now with new HCV medicines building momentum and shaping promise to cure millions of CHC patients, there is never a better time to accumulate interest in and shift focus onto other liver diseases. One of the attractive therapeutic areas is to develop medicines for functionally curing chronic hepatitis B, an area of research that has been stuck in the mud for years with frustration and many failures. About 3 months prior to AASLD Live Meeting 2014, in Aug 2014 BMS announced the discontinuation of peginterferon lambda-1a (pegIFN lambda) clinical program in CHC and CHB and removed this experimental drug from its portfolio. Abandoning clinical development of pegIFN lambda in CHC was not a surprising move, given the fact that the current regimens of DAAs achieve >90% SVR12, hence leaving extremely limited room for another drug only available in injectable form. Nevertheless, the Phase 2b results in HBeAg-positive CHB came out with full disappointment. Originally interim analyses suggested that pegIFN lambda led to faster decline of HBV DNA and quantitative HBsAg as well as better tolerability when compared to pegIFN2a at on-treatment week-12 and week-24, raising hope that this might translate into increased efficacy.[41]

Surprisingly, at the end of the treatment, pegIFN lambda showed comparable serologic/virologic response rates to pegIFN2a. At post-dosing week-24, pegIFN2a trumped pegIFN lambda on HBeAg seroconversion rate and key secondary results.[42] The pegIFN lambda development story reflects the challenge of developing novel drugs for CHB. There were only a few HBV drugs reported during the Liver Meeting 2014 and all of these molecules are still at very early clinical development stage. As one of the late-breaking posters, Novira Therapeutics showed results from a Phase 1a safety/PK study for NVR 3-778 in 40 healthy volunteers. NVR 3-778 is a HBV core (capsid) inhibitor with in vitro anti-HBV potency similar to potent NUCs. Overall it's well tolerated at all doses (50-800 mg qd) and a qd dose of >200 mg may enable sufficient drug concentrations for HBV inhibition in CHB patients [43]. Although the abstract stated that "NVR 3-778 may be the first HBV core inhibitor to advance in clinical testing", this may not be true. HEC Pharma in China has already advanced another HBV capsid inhibitor, GLS4 (morphothiadine mesilate) in Phase 2 stage based on news release and partially published data from Phase 1 study [44]. In addition, an HBV entry inhibitor, Myrcludex B has been tested in a Ph2a study. In Cohort A, 40 chronically HBV infected, HBeAg-negative patients (median HBV DNA 4.7 log10 IU/ml) were treated with once daily sc 0.5mg, 1mg, 2mg, 5mg for 12-week and 10mg for 24-week of Myrcludex B (8 patients per dose). A >1log10 HBV DNA decline at week 12 was observed in 6/8 (75%) patients receiving 10mg Myrcludex B. ALT normalized in 22/40 (55%) patients. No significant changes in HBsAg levels occurred. Overall Myrcludex B is safe and well tolerated in CHB patients.[45]

Arrowhead Research Corp reported Phase 2a results of ARC-520, an siRNA-based therapeutic in HBeAg-negative adult CHB patients receiving long-term treatment of entecavir. Single escalating doses of ARC-520 at 1 mg/kg (cohort 1, 8 patients), 2 mg/kg (cohort 2, 8 patients) and 3 mg/kg (cohort 3, 6 patients, recruitment in progress) were evaluated for up to Day 85. For Cohort 1 patients receiving ARC-520, mean nadir HBsAg was -39% with a mean change of -31% days 85. For cohort 2 patients receiving ARC-520, mean nadir HBsAg was –51% with a mean change on day 85 of -22%. For cohort 2, the percent reduction in HBsAg reached statistical significance vs. placebo for Days 3 through Day 43 post dose. While this is the

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first time demonstration that a reduction in HBsAg mediated through RNA interference was achievable in CHB patients, the decline of HBsAg appeared to be modest. A multi-dose efficacy studies is being planned.[46]

Another siRNA drug, ALN-HBV is being developed by Alnylam. A proof-of-concept study was conducted in chronically-infected chimpanzees (n=4) treated with siRNA targeting a conserved HBV region. The experimental drug was formulated as lipid nanoparticle (LNP). When administered as a single IV dose at 0.25 mg/kg, ALN-HBV triggered a mean 1.9 log10 decrease in viral DNA. The effect appeared RNAi-specific when compared to the control siRNA-LNP, which was administered after the washout period of > 60 days. In multiple ascending dose study of chronically-infected chimpanzee, doses at 0.125 to 0.5 mg/kg achieved mean reductions of 2.9 log10 in HBV DNA and 2.0 log10 in quantitative HBsAg. Interestingly, 2 animals showed ALT flare at 1-2 month post dosing that correlated with the increased expression of interferon gamma (IFNγ) and interleukin-6 (IL-6) in liver, suggestive of an immune clearance of infected hepatocytes. Based on this promising chimpanzee study, a therapeutic RNAi candidate, ALN-HBV, specifically formulated for SC administration is being optimized and characterized for further clinical development.[47]

Gilead is evaluating a Toll-like receptor 7 (TLR7) agonist, GS-9620 in Phase 2 study. Preclinical models in chimpanzee (N=3) and woodchuck (n=7) demonstrated that GS-9620 induced an intrahepatic cytotoxic T cell gene signature in chronically infected animals, suggesting that this is a key mechanism of antiviral response to GS-9620 in both chimpanzee and woodchuck models of CHB.[48] In addition, the induction of B cell and plasma cell transcription signature by GS-9620 in chimpanzee model also indicated that induction of a strong intrahepatic B cell response may also have implication in HBsAg seroconversion.[48] Another early anti-HBV compound, REP 2139-Ca is a nucleic acid-based polymer of HBV release inhibitor that is being developed by REPLICor. REP 2139-Ca is being tested in a Phase 2 study in combination with pegIFN2a in patients with co-infection of hepatitis B / hepatitis D viruses (HBV/HDV). However, there was no data announcement regarding this compound at the Liver Meeting 2014. Previously REPLICor reported clinical data for REP 9AC' at AASLD Liver Meeting 2012.[49] It is unclear how REP 2139-Ca is related to REP 9AC'.

In recent years, advances in understanding the role of immune checkpoint in chronic viral infection have uncovered that a crucial aspect of immune tolerance in CHB has been attributed to high levels of expression of programmed death 1 (PD-1) and its ligand (PD-L1/B7-H1) on viral antigen-specific T-cells and antigen-presenting cells (APCs).[50-52] Blocking the PD-1/PD-L1 interaction in vitro reversed exhausted cytokine production and proliferation of these HBV specific T cells.[53-55] This approach has been generating striking results in immuno-oncology area. Currently BMS is conducting a Phase 1b multiple ascending dose study to investigate the safety, immuno regulatory activity, and preliminary antitumor activity of nivolumab (an anti-PD-1 antibody) in hepatocellular carcinoma (HCC) patients (ClinicalTrials.gov Identifier: NCT01658878). These patients are stratified into HCC with no chronic viral hepatitis, HCC with either CHB or CHC. The change in HCV RNA or HBV DNA during the study can be readily evaluated as proof-of-concept for utilizing this approach in CHB treatment.

Conclusion

To summarize, after HCV/CHC, there is still HBV/CHB affecting 240 million people world-wide. Furthermore, there is still huge unmet medical need in nonalcoholic steato hepatitis (NASH) with no approved drug. Finally, there is still hepatocellular carcinoma among which many cases are caused by chronic HBV or HCV infection. The discovery and clinical development of new medicines in these diseases is both challenging and exciting as well as potentially huge rewarding.

Conflicts of interest

Yonghong Zhu is a Takeda Pharmaceuticals, Inc. employee and owns Takeda stocks and options.

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