Special Contribution

Highlights of the 2012 American Association for the Study of Liver Diseases Meeting

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The American Association for the Study of Liver Diseases (AASLD) held its annual meeting from November 9, 2012, through November 13, 2012, in Boston, Massachusetts. Hepatitis C virus (HCV) was prominently featured in the meeting, reflecting the rapid pace at which new developments in the field of HCV treatment are being introduced. HCV was the topic of an estimated 451 of the 2051 submitted abstracts (22%), with 148 abstracts (7.2%) focused on investigational drugs; it was also the topic of 1 presidential plenary session (top oral abstracts), 1 symposium, 10 of 37 parallel sessions (oral abstracts), and 1 debriefing session at the close of the meeting. This article will summarize some of the major findings presented at the meeting.

Abstracts

The results of studies of several interferon alfa-free regimens were presented as interim analyses (Table 1). Kowdley[1] presented data comparing combinations of the investigational NS3 protease inhibitor ABT-450 (boosted with ritonavir), the investigational NS5A inhibitor ABT-267, the investigational NS5B nonnucleoside polymerase inhibitor ABT-333, and ribavirin for a period of 8, 12, or 24 weeks, in patients who had HCV infection genotype 1 and did not have cirrhosis. Only data on the 8- and 12-week regimens were reported at this meeting. Intent-to-treat sustained virologic response (SVR) rates 12 weeks after cessation of treatment (SVR12) were 85.4% to 97.5% among treatment-naive patients, with the 12-week, 5-drug regimen performing the best. Among patients with prior null response, SVR12 rates were 88.9% to 93.3%. The 5-drug regimen has been selected for phase III trials.

Interim data on combination therapy with the investigational NS5a inhibitor daclatasvir, the investigational nucleotide polymerase inhibitor sofosbuvir, and ribavirin were presented by Sulkowski.[2] All patients were naive to treatment and did not have cirrhosis. Because daclatasvir and sofosbuvir each have pangenotypic activity, the study enrolled subjects in 2 stages. Stage 1 evaluated 24 weeks of daclatasvir and sofosbuvir, with or without ribavirin, for patients with HCV genotypes 1, 2, or 3; stage 2 evaluated 12 weeks of daclatasvir and sofosbuvir, with or without ribavirin, for patients with HCV genotype 1 only. Stage 1 also included an arm with a 4-week sofosbuvir lead-in. Results were presented by genotype as intent-to-treat, with missing data equal to failure. For patients with HCV genotypes 2 and 3, SVR rates 24 weeks after cessation of treatment (SVR24) were 88% to 100%. Notably, the number of patients in each treatment group was small (see Table 1). There were only 2 confirmed virologic failures in stage 1, both occurring in the sofosbuvir lead-in group. The other patients who did not achieve SVR were lost to follow up. Among patients with HCV genotype 1, SVR24 rates were 100% in both the ribavirin and no ribavirin groups. The SVR24 rate in the sofosbuvir lead-in group was 14 of 15 (93%) in patients with HCV genotype 1. The only patient without an SVR had a virus with a different genetic sequence, consistent with reinfection.

Daclatasvir was also studied as part of an interferon alfa-free regimen in patients with HCV genotype 1, as reported by Everson.[3] In this phase IIa study, daclatasvir was used in combination with the investigational NS3 protease inhibitor asunaprevir and the investigational nonnucleoside polymerase inhibitor BMS-791325. All patients in the study had HCV genotype 1 and did not have cirrhosis. The study evaluated 2 different doses of the polymerase inhibitor as well as 12- versus 24-weeks of treatment. Only the results with the lower dose (75 mg) of BMS-791325 were presented. The SVR 4 weeks after cessation of treatment (SVR4) for both the 12- and 24-week groups was 94%, with all non-SVRs due to missing data. The SVR12 data were only available for the 12-week group, and was 94%.

The largest interferon alfa-free trial conducted to date has been the SOUND-C2 (Safety and Antiviral Effect of Oral Combinations Without Interferon in Patients Diagnosed With Chronic Hepatitis C) trial, the final results of which were presented by Zeuzum.[4] This open-label, randomized study had 5 treatment arms that evaluated the investigational NS3/4A protease inhibitor faldaprevir in combination with the investigational nonnucleoside NS5B inhibitor BI 207127, with or without ribavirin. The SVR12 results were 52% to 69% in the arms containing ribavirin. No statistical analysis was provided regarding any differences between groups. When ribavirin was removed from the treatment regimen SVR12 rates dropped to 39%. Faldaprevir in combination with BI 207127 600 mg, twice daily, plus ribavirin has moved into phase III trials. Subanalysis of results by HCV genotype subtype (1a versus 1b) showed that genotype 1b responded much better than genotype 1a across all treatment arms. In the small number of patients with

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Table 1. Selected Investigational Interferon Alfa-Free Regimens Reported at the 2012 American Association for the Study of Liver Diseases Meeting

Abstract Number/Study (Presenter)	N	Study Population Treatment Experience, HCV Genotype	Protease Inhibitor	Polymerase Inhibitor	NS5A Inhibitor	Other Drug	Duration (Weeks)	SVR
LB-1 (Kowdley)	80	Naive, 1	ABT-450/r[a]	ABT-333	ABT-267	Ribavirin	8	87.5%
	41	Naive, 1	ABT-450/r	ABT-333		Ribavirin	12	85.4%
	79	Naive, 1	ABT-450/r		ABT-267	Ribavirin	12	89.9%
	79	Naive, 1	ABT-450/r	ABT-333	ABT-267		12	87.3%
	79	Naive, 1	ABT-450/r	ABT-333	ABT-267	Ribavirin	12	97.5%
	45	Null, 1	ABT-450/r		ABT-267	Ribavirin	12	88.9%
	45	Null, 1	ABT-450/r	ABT-333	ABT-267	Ribavirin	12	93.3%
LB-2 (Sulkowski)	16	Naive, 2/3		Sofosbuvir w/ lead-in	Daclatasvir		24	88%
	14	Naive, 2/3		Sofusbuvir	Daclatasvir		24	100%
	14	Naive, 2/3		Sofosbuvir	Daclatasvir	Ribavirin	24	93%
	15	Naive, 1		Sofosbuvir w/ lead-in	Daclatasvir		24	93%
	14	Naive, 1		Sofosbuvir	Daclatasvir		24	100%
	15	Naive, 1		Sofosbuvir	Daclatasvir	Ribavirin	24	100%
LB-3 (Everson)	16	Naive, 1	Asunaprevir	BMS-791325 75 mg daily	Daclatasvir		12	94% SVR12
	16	Naive, 1	Asunaprevir	BMS-791325 75 mg daily	Daclatasvir		24	94% SVR4
232/SOUND-C2 (Zeuzem)	81	Naive, 1	Faldaprevir	BI-207127 600 mg TID		Ribavirin	16	59%
	80	Naive, 1	Faldaprevir	BI-207127 600 mg TID		Ribavirin	28	59%
	77	Naive, 1	Faldaprevir	BI-207127 600 mg TID		Ribavirin	40	52%
	78	Naive, 1	Faldaprevir	BI-207127 600 mg BID		Ribavirin	28	69%
	46	Naive, 1	Faldaprevir	BI-207127 600 mg TID			28	39%
231/ZENITH (Jacobson)	18	Naive, 1	Telaprevir	VX-222			12	Arm discontinued[b]
	29	Naive, 1	Telaprevir	VX-222			12	Arm discontinued[b]
	23	Naive, 1a	Telaprevir BID	VX-222		Ribavirin	12	5/5[c]
	23	Naive, 1b	Telaprevir BID	VX-222		Ribavirin	12	4/6[c]
212 (Sulkowski)	46	Naive, 1	GS-9451	Tegobuvir	GS-5885 30 mg QD	Ribavirin	24	67%[d]
	94	Naive, 1	GS-9451	Tegobuvir	GS-5885 90 mg QD	Ribavirin	12	68%[d]
							24	81%[d]
229/ELECTRON (Gane)	11	Naive, 2/3		Sofosbuvir		Ribavirin	12	100%
	10	Naive, 2/3		Sofosbuvir			12	60%
	25	Naive, 2/3		Sofosbuvir		Ribavirin 800	12	60%
	25	Naive, 2/3		Sofosbuvir		Ribavirin	8	64%
	25	Experienced, 2/3		Sofosbuvir		Ribavirin	12	68%
	25	Naive, 1		Sofosbuvir		Ribavirin	12	84%
	10	Null, 1		Sofosbuvir		Ribavirin	12	10%
	25	Naive, 1		Sofosbuvir	GS-5885	Ribavirin	12	100%
	10	Null, 1		Sofosbuvir	GS-5885	Ribavirin	12	100%
81/MATTERHORN (Feld)	23	Partial, 1b	Danoprevir/r[a]	Mericitabine		Ribavirin	24	39%
	31	Null, 1b	Danoprevir/r	Mericitabine		Ribavirin	24	55%

BID indicates twice per day; QD, once per day; SVR, sustained virologic response; SVR4, sustained virologic response 4 weeks after cessation of treatment; SVR12, sustained virologic response 12 weeks after cessation of treatment; TID, three times per day. Data drawn from Kowdley et al,[1] Sulkowski et al,[2] Everson et al,[3] Zeuzem et al,[4] Jacobson et al,[5] Sulkowski et al,[6] Gane et al,[7] Feld et al.[8]

[a] Ritonavir used as booster.

[b] Discontinued due to high failure rate.

[c] Those who were detectable at week 2 or 8 received 24 additional weeks of peginterferon alfa and ribavirin.

[d] Only patients who achieved negative HCV RNA at week 2 continued. Remainder had peginterferon alfa and ribavirin added.

cirrhosis that were included in the study, 33 of 362, SVR12 rates were similar between patients with cirrhosis and those without cirrhosis across all treatment groups.

Several other abstracts reported results from trials of interferon alfa-free regimens (Table 1). In the ZENITH trial,[5] the combination of telaprevir and VX-222, an investigational nonnucleoside polymerase inhibitor, had a high virologic breakthrough rate and the study arm was discontinued. The addition of ribavirin to the regimen improved the results slightly, but most patients still required the addition of peginterferon alfa.

Sulkowski[6] presented data from the all-oral combination of the investigational protease inhibitor GS-9451, the investigational nonnucleoside polymerase inhibitor tegobuvir, and the investigational NS5A inhibitor GS-5885, in combination with ribavirin. Only those patients who achieved a very rapid virologic response (vRVR, negative HCV RNA level at week 2) were eligible to continue with all-oral therapy (72%-79% of patients). In remaining patients peginterferon alfa was added. Those who were eligible to remain on oral therapy had an SVR rate of 67% to 81%. Gane presented additional interim results from the ELECTRON trial,[7] a multi-arm study of the nucleotide analogue polymerase inhibitor sofosbuvir for patients with HCV genotypes 1, 2, and 3. Previous results from this study showed 100% SVR rates with sofosbuvir and ribavirin, with or without peginterferon alfa, in treatment-naive patients with HCV genotypes 2 or 3. However, when the duration of treatment was shortened to 8 weeks, sofosbuvir monotherapy was used, low-dose (rather than weight-based) ribavirin was used, or patients were treatment-experienced, the SVR rates dropped. Lower response rates were also seen in patients with genotype 1 HCV, but the rates were improved to 100% with the addition of the NS5A inhibitor GS-5885 to the regimen of sofosbuvir and ribavirin, even among patients with prior null response. All arms of this study were small (10 patients or fewer). Finally, Feld presented

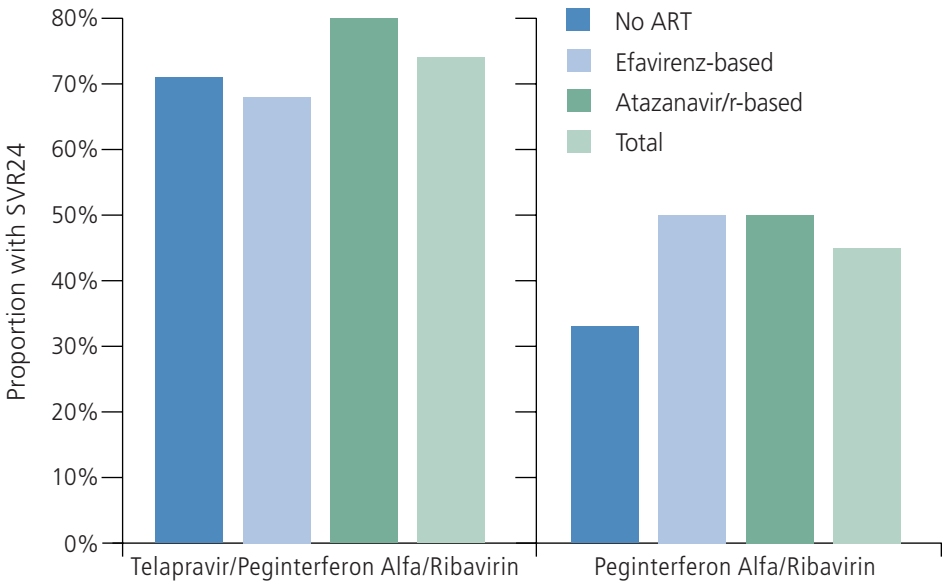

Figure. Sustained virologic response (SVR) 24 weeks after cessation of treatment (SVR24) rates for HIV/hepatitis C virus coinfected patients treated with telaprevir/peginterferon alfa/ribavirin compared with control of peginterferon alfa/ribavirin by antiretroviral drug-based therapy. ART indicates antiretroviral therapy; /r, ritonavir.

data from the MATTERHORN study[8] of the protease inhibitor danoprevir, the nucleoside analogue polymerase inhibitor mericitabine, and ribavirin in patients with previous partial or null responses. The virologic breakthrough rates were high in patients with HCV genotype 1a, who were all rolled over into peginterferon alfa-containing arms of the study. Among patients with HCV genotype 1b, SVR rates were 39% to 55%, but were higher when interferon alfa was used.

Final results from the phase IIb study of telaprevir in HIV/HCV-coinfected patients were presented by Sulkowski as well.[9] The study enrolled patients with HCV genotype 1, naive to therapy, whose CD4+ counts were greater than 300 cells/μL if on antiretroviral drugs, or greater than 500 cells/μL if antiretroviral therapy-naive. Patients with cirrhosis were allowed in the study if the cirrhosis was compensated. Patients were randomized to receive telaprevir, peginterferon-alfa 2a, and ribavirin for 12 weeks, followed by peginterferon alfa-2a and ribavirin for an additional 36 weeks, or peginteferon alfa-2a and ribavirin for 48 weeks (control group). Patients could be antiretroviral treatment-naive or on stable, predefined antiretroviral therapy of combination tenofovir/emtricitabine/efavirenz or tenofovir/emtricitabine/atazanavir/ritonavir. If efavirenz was used, the dosage of telaprevir was increased to 1125 mg 3 times daily. In the antiretroviral-naive, efavirenz-based, and atazanavir-based groups, SVR24 rates were 71%, 69%, and 80% respectively (Figure). Corresponding rates in the control group were 33%, 50%, and 50%. As seen in trials with monoinfected patients who were given telaprevir, rash was more common in the telaprevir group than in control groups (29% and 18%, respectively) as was pruritus (34% and 5%, respectively). The incidence of anemia was not higher with telaprevir use and no HIV breakthroughs were seen. The SVR rates with telaprevir are similar to the historical response rates seen in monoinfected HCV patients treated with telaprevir. The SVR rates in the control groups in this study are higher than previously seen in HIV-coinfected patients.

One disadvantage of the currently available HCV protease inhibitors is their thrice-daily administration. The OPTIMIZE trial[10] provides data supporting the twice-daily administration of telaprevir in treatment-naive patients. In this phase III study 371 patients were randomized to receive telaprevir 750 mg every 8 hours and 369

patients were randomized to receive telaprevir 1125 mg every 12 hours, each in combination with peginterferon alfa-2a and ribavirin. SVR12 rates were comparable between the 2 groups by intent-to-treat analysis (73% in the every 8-hour group and 74% in the every 12-hour group) and per protocol analysis, meeting the predefined criteria for noninferiority. The adverse event profile was similar between the 2 arms. No change in the product prescribing information has been approved by the US Food and Drug Administration (FDA) at this time.

Although interferon alfa-free regimens are promising, these regimens are still perhaps 2 years to 4 years from approval. A novel investigational interferon, peginterferon lambda-1a, has now entered phase III trials. Data from the Phase II EMERGE trial[11] were presented by Muir. In this trial, peginterferon lambda-1a was compared with peginterferon alfa-2a in 407 treatment-naive patients with HCV genotype 1 who did not have cirrhosis. Patients receiving peginterferon lambda had similar SVR rates to those receiving peginterferon alfa (37.3% and 36.9%, respectively), but experienced fewer hematologic adverse effects, myalgias, pyrexia, arthralgia, and chills. There were also fewer dosage reductions in either the interferon or ribavirin in the peginterferon lambda group. Peginterferon lambda is being further evaluated in combination with direct-acting drugs.

The association between the IL28B CC genotype and patient response to interferon alfa has been well-established.[12-14] Studies of direct-acting drugs have shown that the IL28B CC genotype has been less useful in predicting response, but may still play some role in predicting those likely to have SVR. In a study presented by Thompson,[15] patients with the IL28B CC genotype were enrolled and vRVR was used to select patients with HCV genotype 1 for a 6-week course of treatment. Patients who had a vRVR (negative HCV RNA at week 2) were randomized to receive either 6 weeks or 12 weeks of the NS5A inhibitor GS-5885, the protease inhibitor GS-9451, peginterferon alfa, and ribavirin. Ninety-four percent of patients in the study achieved vRVR. The SVR12 rates in the 6-week arm were 81%, and were 100% in the 12-week arm. These preliminary study data showed that in select patients, a regimen as short as 6 weeks could produce a high SVR rate.

Conclusion

This is an exciting time for HCV therapeutics. The next few years may bring many new drugs, and regimens that are interferon alfa-free, with higher response rates, fewer adverse effects, and shorter durations of treatment. Patients with cirrhosis and those with null response have traditionally been difficult to treat, but preliminary data suggest that high response rates are achievable even in these populations. Current challenges include when to treat immediately and when to defer treatment in those with mild liver disease who can afford to wait for newer drugs. Data reported on new drugs and regimens in special populations, such as HIV-coinfected patients or liver transplant recipients, are limited. However, in the near future, rapid growth should be witnessed in the armamentarium of options for treatment of HCV infection.

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