Incivek, Victrelis Studies Hint at Superior Cure Rates in HIV/HCV Coinfection

March 6, 2012 By Tim Horn

Adding a protease inhibitor to pegylated interferon and ribavirin as part of hepatitis C virus (HCV) treatment resulted in higher sustained virologic response rates 12 weeks after finishing the regimen, pointing to significantly higher cure rates compared with those receiving pegylated interferon and ribavirin alone, according to results from two Phase II studies presented Tuesday, March 6, at the 19th Conference on Retroviruses and Opportunistic Infections in Seattle.

With Merck's Victrelis (boceprevir), 60 percent of people living with HIV and hepatitis C coinfection had undetectable HCV viral loads 12 weeks after finishing 48 weeks of treatment. With Vertex's Incivek (telaprevir), 74 percent of coinfected study participants had undetectable HCV viral loads 12 weeks after they finished treatment.

If HCV viral loads rebound after successfully completing a course of treatment, they usually do so within the first few weeks after stopping therapy. In turn, undetectable HCV levels after 12 weeks of stopping therapy, known as SVR-12, are believed to be highly predictive of the ultimate goal: a viral cure, defined as a viral load that doesn't rebound within 24 weeks, also known as SVR-24, as in "sustained virologic response for 24 weeks."

Approval of the HCV protease inhibitors for people coinfected with HIV and hepatitis C requires successful completion of studies involving this distinct population of individuals, who historically have been significantly less likely to be cured of their hepatitis using longtime standard therapy of pegylated interferon plus ribavirin.

Encouragingly, the SVR-12 data in people living with HIV and HCV coinfection are similar to efficacy data seen in clinical trials involving people living with HCV but not HIV. According to studies that contributed to the drugs' approvals in May, roughly 70 percent of HCV-positive individuals were found to meet the SVR-24 goal.

Incivek for HIV/HCV Coinfection

Douglas Dieterich, MD, of Mount Sinai School of Medicine in New York presented the Incivek data. The clinical trial is a two-part Phase II randomized, placebo-controlled trial involving people living with HIV coinfected with genotype 1 HCV and starting hepatitis C treatment for the first time.

The study enrolled 62 people, 60 of whom received at least one dose of the study drug and were included in the analysis reported by Dieterich. People in the first and second part of the study—Part A and Part B—were allotted to receive either 12 weeks of Incivek or placebo in combination with Pegasys (pegylated interferon) plus ribavirin followed by an additional 36 weeks of Pegasys/ribavirin alone.

Doug Dieterich, MD, at the 19th Conference on Retroviruses and Opportunistic Infections in Seattle.
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Part A enrolled 13 people who were not receiving antiretroviral (ARV) therapy. Part B enrolled 47 people receiving ARV therapy—either Atripla (efavirenz/emtricitabine/tenofovir) or Norvir (ritonavir)–boosted Reyataz (atazanavir) plus Truvada (emtricitabine/tenofovir). It's important to note that those using Atripla took a higher dose of telaprevir—1,125 milligrams (mg) three times daily instead of the standard 750 mg dose three times a day—because of a known drug interaction between efavirenz and Incivek.

By the end of the 48-week on-treatment period, 25 people had discontinued treatment, nine of whom stopped because of predefined stopping rules (two of them were in the Incivek study arm).

Eighty-five percent of the study subjects were male, 69 percent were white, and the average age was 45 years old. About 68 percent had HCV genotype 1a—the more difficult of the two HCV genotypes to treat—and most had HCV viral loads in excess of 800,000 copies. Ten percent of the participants had advanced liver fibrosis, documented by liver biopsies.

The results, detailing on-treatment responses at weeks 4, 12 and 24, and at 12 weeks after treatment completion, are summarized in the table below. All time points are important. An undetectable viral load at four weeks, known as a rapid virologic response (RVR), is believed to be highly predictive of an SVR, provided that HCV viral load remains undetectable for the remaining 44 weeks. An undetectable viral load at 12 weeks, known as a complete early virologic response (cEVR), is also valuable; if HCV is still detectable (or hasn't decreased by at least 2 log) by this time point, an SVR is unlikely. If HCV viral load remains detectable after 24 weeks of therapy, the stopping rule is applied and all treatment is discontinued.

	Part A	Part B	Total					
No ARV Treatment	Atripla	Norvir-Boosted Reyataz						
HCV Undetectable	Incivek Group	Control Group	Incivek Group	Control Group	Incivek Group	Control Group	Incivek Group	Control Group
4 weeks	71%	0%	75%	0%	60%	0%	68%	0%

12 weeks	86%	33%	88%	25%	67%	25%	79%	27%
24 weeks	86%	33%	75%	50%	67%	75%	74%	55%
SVR-12	71%	33%	69%	50%	80%	50%	74%	45%

During treatment, virologic failure was reported in three people (8 percent) in the Incivek group. Two of these patients were on Atripla, and one was on Norvir-boosted Reyataz plus Truvada. In the control arm, 36 percent experienced on-treatment virologic failure.

At the end of treatment, HCV viral loads were detectable in 14 percent of those in the Incivek groups, compared with 41 percent of those in the control groups. Of note, viral load rebounds following discontinuation of therapy occurred in 3 percent of those in the Incivek groups, compared with 15 percent of those in the control groups.

CD4 cell counts tended to decrease in all of the study groups, which is a common issue during hepatitis C treatment. However, the CD4 percentage remained stable. No HIV viral load rebounds have been documented in the ARV study arms.

A number of side effects were more common—occurring at least 10 percent more often—among those receiving Incivek plus Pegasys and ribavirin, compared with those receiving Pegasys/ribavirin alone. These included itching, headache, nausea, skin rash, fever and depression. Weight loss and insomnia were more likely to be seen in those using pegylated interferon/ribavirin alone. Of note, none of the study participants experienced severe rash, although mild or moderate skin rash was reported in 34 percent of the Incivek recipients and 23 percent of those who took pegylated interferon/ribavirin alone.

Serious anemia occurred in 11 people, or 29 percent, of those in the Incivek group. Three of them were treated with red blood cell growth factors, and four received blood transfusions. Among those who received Pegasys/ribavirin alone, 23 percent—or five people—developed serious anemia; one was treated with red blood cell growth factor, and one was given a transfusion.

Vertex’s planned Phase III study is now open. The study will evaluate 24- and 48-week response-guided therapy—using RVR and EVR rates to determine the length of treatment—using Incivek combination therapy in people coinfected with both viruses who are new to treatment for hepatitis C or who experienced HCV viral loads rebounds after successfully completing at least one earlier course of therapy with pegylated interferon and ribavirin alone.

The study will also include coinfected individuals who didn’t respond to an earlier course of treatment—dubbed partial responders and null responders—though they will be treated with a full 48-week course of either pegylated interferon/ribavirin alone or Incivek-based treatment.

Victrelis for HIV/HCV Coinfection

Mark Sulkowski, MD, at the 19th Conference on Retroviruses and Opportunistic Infections in Seattle.
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{PS..7} Results from the Victrelis HIV/HCV coinfection study were reported by Mark Sulkowski, MD, of Johns Hopkins University School of Medicine and his colleagues. The study enrolled 100 people with HIV and genotype 1 HCV infection who hadn't yet been treated for hepatitis C.

As per the approved Victrelis dosing schedule, all study volunteers began therapy with a four-week lead-in period in which pegylated interferon/ribavirin was used alone. From there, about two thirds of the study volunteers received 800 mg of Victrelis three times daily combined with once-weekly Peg-intron (pegylated interferon) injections and twice-daily ribavirin for the study's remaining 44 weeks. However, participants with detectable HCV viral loads and less than a 2 log viral load decline at treatment week 12, or detectable HCV viral load at treatment week 24, were considered treatment failures, and they discontinued all treatment.

Sixty-nine percent of the study subjects were male, 82 percent were white, and the average age was 43. About 65 percent had HCV genotype 1a, and most of them had HCV viral loads in excess of 800,000 copies. Five percent of the people enrolled had advanced liver fibrosis, as documented with liver biopsies.

All coinfected participants were taking antiretroviral therapy, which was mostly limited to specific Norvir-boosted protease inhibitor-based regimens, because of known drug-drug interactions between Victrelis and various HIV medications. However, one study participant was taking Selzentry (maraviroc), another was taking Atripla, and four were using Isentress (raltegravir).

The results, detailing treatment responses at 4, 8, 12, 24 and 48 weeks—as well as SVR-12 rates—are summarized in the table below.

HCV Undetectable	Victrelis Group	Control Group	Victrelis Group vs. Control Group
4 weeks	4.7%	8.8%	(4.1%)
8 weeks	37.5%	14.7%	22.8%
12 weeks	56.5%	25.0%	31.5%
24 weeks	70.5%	34.4%	36.1%
48 weeks	65.6%	29.4%	36.2%

SVR-12	60.7%	26.5%	34.2%

During treatment, HIV viral loads became detectable in 3 of 64 people in the Victrelis group and 4 of 34 patients in the control group. In the Victrelis group, two of the people who had detectable HIV viral loads were taking Norvir-boosted Reyataz plus Truvada and one was taking Kaletra (lopinavir/ritonavir) plus Truvada.

The most common side effects—with a difference of equal to or greater than 10 percent among those receiving Victrelis plus pegylated interferon/ribavirin, compared with pegylated interferon/ribavirin alone—were anemia, low neutrophil counts, bad taste (dysgeusia), vomiting, diarrhea, fevers, headache, fatigue and decreased appetite. Of note, mild-to-moderate side effects were more common among those treated with triple therapy than pegylated interferon/ribavirin, with the exception of flu-like symptoms.

Serious side effects—low neutrophil counts and anemia—were more common in people who were treated with triple therapy. Low neutrophil counts were more than twice as common—27 percent versus 12 percent—in the Victrelis group. Overall, 3 percent of the control arm developed serious anemia; 21 percent of them were treated with red blood cell growth factor, and 6 percent were transfused. In the Victrelis arm, 5 percent developed serious anemia; 38 percent were treated with red blood cell growth factor, and 6 percent were transfused.

In addition to this ongoing Phase II study in coinfected participants new to HCV treatment, Merck is collaborating with the French National Agency for Research on AIDS and Viral Hepatitis (ANRS) on an ongoing Phase II study in people who failed previous HCV treatment.

The company also plans to begin a Phase III coinfection study for Victrelis-based combination therapy later this year in collaboration with the federally funded AIDS Clinical Trials Group (ACTG).
