Incivek, Victrelis Working Well in HIV/HCV Coinfection Studies

November 9, 2011

Roughly 70 percent of people living with HIV and hepatitis C virus (HCV) coinfection have undetectable HCV viral loads after 24 weeks of treatment with either Incivek (telaprevir) or Victrelis (boceprevir) plus pegylated interferon and ribavirin, according to interim results from two studies reported at two recent medical conferences.

Though final proof of the drugs' effectiveness won't be known until hepatitis C treatment is stopped and all coinfected people in the trials are followed for an additional six months, rates of undetectable viral loads among those using triple-drug treatment are currently 16 percent to 36 percent above those using only pegylated interferon and ribavirin.

In May 2011, the U.S. Food and Drug Administration (FDA) approved both Vertex Pharmaceuticals' Incivek and Merck's Victrelis for HIV-uninfected people living with HCV genotype 1 to use in combination with pegylated interferon and ribavirin. According to studies that contributed to the drugs' approvals, roughly 70 percent of HCV-positive individuals were sustained virologic responders (SVRs)—cured of their infection—six months after completing treatment.

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. Phase II study data are now beginning to trickle in.

Incivek for HIV/HCV Coinfection

Kenneth Sherman, MD, of the University of Cincinnati College of Medicine and his colleagues reported a study at the 62nd annual meeting of the American Association for the Study of Liver Diseases on Monday, November 7, in San Francisco. The study is a two-part Phase II randomized, placebo-controlled trial involving HIV-positive people coinfected with genotype 1 HCV 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 interim analysis.

People in the first and second part of the study—Part A and Part B—were allotted to receive either 12 weeks of telaprevir or placebo in combination with Pegasys (pegylated interferon) plus ribavirin followed by an additional 36 weeks of Pegasys/ribavirin alone.

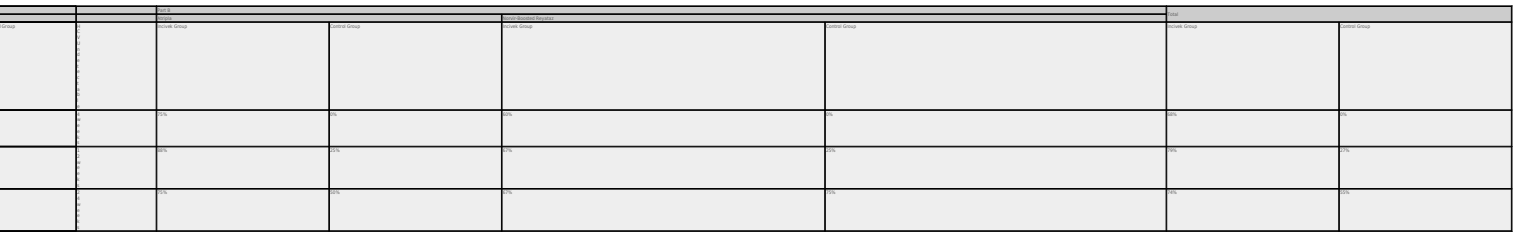
Part A enrolled 13 people who were not receiving antiretroviral (ARV) therapy. Part B enrolled 47 people receiving ARV therapy—either Atripla (efavirenz/emtricitabine/tenofovir) or Norvir (ritonavir)–boosted Reyataz (atazanavir) plus Truvada (emtricitabine/tenofovir). It's important to note that those 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 telaprevir.

The interim analysis, reported by Sherman's team, involved 44 participants who had reached week 24 of treatment. Sixteen people discontinued before week 24 of study treatment, six of whom stopped because of predefined stopping rules.

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, as documented with liver biopsies.

The results, detailing treatment responses at 4, 12 and 24 weeks, 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, all treatment is discontinued.



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

A number of side effects were more common—occurring at least 10 percent more often—among those receiving telaprevir plus pegylated interferon/ribavirin, compared with those receiving pegylated interferon/ribavirin alone. These included itching, headache, nausea, skin rash, fever and depression. Weight loss was more likely to be seen in those using pegylated interferon/ribavirin alone.

Vertex's planned Phase III study is expected to begin enrollment by the end of 2011. 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 relapsed after at least one earlier course of therapy

with pegylated interferon and ribavirin alone. Participants who had not responded to an earlier course of treatment (partial responders and nulls) will receive 48 total weeks of Incivek-based treatment.

Victrelis for HIV/HCV Coinfection

Twenty-four week data from the Victrelis HIV/HCV coinfection study were reported by Mark Sulkowski, MD, of Johns Hopkins University School of Medicine and his colleagues on October 22 at the 49th annual meeting of the Infectious Disease Society of American (IDSA) in Boston. 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 years old. 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 limited to specific Norvir-boosted protease inhibitor-based regimens, because of known drug-drug interactions between Victrelis and various HIV medications.

The results, detailing treatment responses at 4, 8, 12 and 24 weeks, 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%

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 low neutrophil counts, bad taste (dysgeusia), vomiting, fevers,

headache and decreased appetite. Of note, however, the rate of serious side effects was nearly three times more common among those receiving pegylated interferon/ribavirin alone compared with Victrelis plus pegylated interferon/ribavirin.

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).

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