Hot News

Prompt Arrival of Antivirals against Hepatitis C for HIV Patients

The recent release of the phase III results of the new protease inhibitors (telaprevir, boceprevir) developed against HCV has been a major event in the field. The figures below depict the rate of sustained virologic response (SVR) using these drugs in combination with peginterferon plus ribavirin. On appropriate treatment schedules, 75% of genotype 1 subjects treated with telaprevir and 68% of those treated with boceprevir will be cured. Although the rates in patients with prior failure to interferon-based therapies are lower, they are still good, particularly in the subset of prior relapsers, going down to of 20-25% in prior nonresponders.

The current situation in HCV therapeutics recalls the summer of 1996, when the report of the first trials using HIV protease inhibitors (saquinavir, indinavir, ritonavir) revolutionized the AIDS field. Expanded-access programs for both telaprevir and boceprevir will begin in early 2011 and final approval by regulatory agencies is expected for the next summer.

The new direct-acting antivirals (DAA) against HCV are orally prescribed in contrast with peginterferon, which has to be given subcutaneously once a week. However, the new DAA display a low genetic barrier for resistance and, as in HIV, have to be given as part of combination therapy, which at this time is the backbone of peginterferon plus ribavirin.

There are significant differences between the first-generation (covalent) HCV protease inhibitors. Telaprevir will most likely receive approval to be used twice-daily, while boceprevir will require trice-daily administration. Telaprevir will be given for only the first 12 weeks of combination therapy, whereas boceprevir will be provided for the whole treatment period. While triple-drug combination with telaprevir will be given from the first day, a lead-in phase of four weeks with peginterferon/ribavirin alone will be advisable before adding boceprevir.

Both telaprevir and boceprevir are relatively well tolerated, with anemia being a common side effect. Also, telaprevir is often associated with a skin reaction whose rate increases with the length of exposure to the drug, affecting a third of patients by week 12.

It must be highlighted that telaprevir and boceprevir will mainly be active against HCV genotype 1, subtype 1b being more robust to resistance than subtype 1a, as result of a polymorphisms at codon 155 at the HCV protease. Drug resistance mutations selected by these compounds in HCV overlap almost entirely, and accordingly, cross-resistance will hamper the opportunities for sequential use of these drugs.

Although the results of trials specifically conducted with telaprevir or boceprevir in HIV/HCV-coinfected individuals are still not available, the relative priority to treat this population will push the authorities to facilitate access to these drugs as soon as possible. The faster progression to cirrhosis and the increased

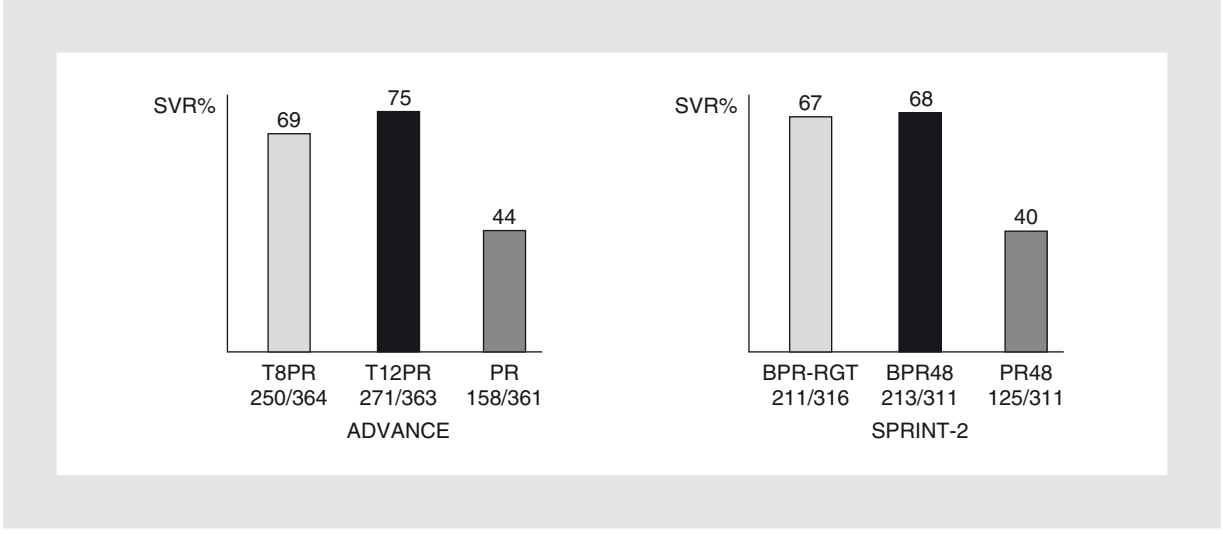

Figure. *Rate of sustained virologic response (SVR) in interferon-naive HCV genotype 1 patients treated with peginterferon (P)-ribavirin (R) plus either telaprevir (T) (ADVANCE trial) or boceprevir (B) (SPRINT-2 trial). In the ADVANCE trial, an arm with only 8 weeks of the drug was tested and found to be suboptimal. In the SPRINT-2 trial, an arm using response-guided therapy (RGT) was tested and found to perform as well as 48 weeks of therapy.*

risk of hepatotoxicity of antiretroviral agents are strong arguments to favor quicker access. One of the main challenges when planning to use DAA in HIV individuals will be the potential for drug interactions. This information is crucial and has to be known before prescribing DAA in subjects receiving antiretroviral agents.

Finally, the arrival of DAA against HCV has opened the question of who should treat hepatitis C in this new era. Until now, hepatologists were the largest group providing care to this population, mainly because limited therapeutic options were available for asymptomatic patients, while the complications of advanced liver disease, including decompensated cirrhosis and hepatocellular carcinoma, were well within their area of expertise. However, as treatment for asymptomatic HCV is moving to the fore, the management of encephalopathy, variceal bleeding or ascites will be kept for only a minority of hepatitis C patients. In replacement, new virologic concepts (viral load and viral kinetics, genotypes and subtypes, resistance and polymorphisms, etc.) will drive treatment decisions, and the expertise from infectious diseases specialists might be more appropriate. At the last American Association for the Study of Liver Diseases (AASLD) conference held in Boston last November, Dr. Paul Pokros (Scripps clinic, La Jolla, CA) suggested that a new figure, the HCV doctor, will emerge as has occurred in the care of HIV/AIDS, where a subset of ID doctors shift to specialize in the complex management of the disease and currently are HIV doctors.

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Do Integrase Inhibitors Impact on the HIV Reservoir?

The introduction of combination antiretroviral treatment has represented a great milestone in the management of HIV-infected individuals, with large benefits in survival and quality of life. The achievement of this landmark has prompted the exploration of further goals, including the eradication of HIV infection once established. Since the biggest problem for eradicating the virus from the organism is the integration of the HIV genome into the host cells, the arrival of integrase inhibitors has renewed the expectations for a cure for AIDS. Several studies have recently explored this hypothesis and their conclusions merit some thoughts.

Treatment intensification with raltegravir, the first approved integrase inhibitor for treating HIV infection, may exert some activity in patients harboring low-level viremia under other antiretroviral agents, an observation without precedent using other antiretroviral medications which did not exert any effect on residual viremia (Dinoso, et al. Proc Natl Acad Sci USA. 2009;106:9403-8). Two studies have evaluated the effect of raltegravir intensification, one after four weeks (McMahon, et al. Clin Infect Dis. 2010;50: 912-9), and another after 12 weeks (Gandhi, et al. PLoS Med. 2010;7:e7). These two studies did not find any significant persistent decline in viremia, indirectly suggesting the classical view that postulates that residual viremia under antiretroviral therapy mainly comes from reservoirs and not from ongoing cycles of HIV replication.

The brain and gut are the anatomic locations where latently HIV-infected cells constitute the major viral reservoir. Consequently, analysis of these particular sites might give more information than studies performed on peripheral blood cells. In a recent report, the effect of treatment intensification with raltegravir was assessed in the gut (Yukl, et al. AIDS. 2010;24:2451-60). Although no effect was recognized on plasma HIV RNA, neither in cells from the blood, duodenum, colon, or rectum, a striking reduction in viremia was noticed in the ileum, one of the richest lymphatic organs, along with CD4 gains.

It should be highlighted that residual viremia in all studies discussed above was measured using assays able to detect up to one HIV RNA copy/ml. Although this threshold is very low, low-level viremia in patients on antiretroviral therapy generally is only 1 log above this threshold and therefore not much window exists to detect significant reductions in residual viremia. Measurement of episomal cDNA has been tried in an attempt to enhance the recognition of any further antiviral activity of drugs used as part of intensification strategies (Buzón, et al. Nat Med. 2010;16:460-5), and transient rises in episomal HIV-DNA after two to four weeks of raltegravir intensification have been considered as evidence of an effect on active HIV replication. However, integrated DNA levels remained stable over time, suggesting that archived HIV DNA is not altered by raltegravir intensification.

Altogether, the lack of a significant recognizable effect of raltegravir intensification on residual plasma viremia and on integrated proviral load suggests that adding raltegravir on top of antiretroviral regimens in patients with undetectable viremia using commercial assays do not impact on residual viral load, even when CD4 gains may occur. Hence, different and novel strategies must be investigated in the search for an eradication of HIV infection. With the current knowledge, efforts must be focused on targeting chronically HIV-infected cells, which constitute by far the largest viral reservoir.

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