ICAAC: Prezista and Aptivus on Drug-Resistant HIV

September 29, 2006 By Tim Horn

Three reports presented Friday at the 46th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) in San Francisco have shed additional light on the benefits of the protease inhibitors (PIs) Prezista™ (darunavir) and Aptivus® (tipranavir) in the treatment of HIV-positive people who have tried and failed combination therapy in the past. One report detailed 96-week follow-up data from two phase III clinical trials of Aptivus; a second report involved a comparison between the phase III clinical trials of Aptivus and Prezista; and a third report looked at the effects of prior treatment with other PIs, including Aptivus, on the response to Prezista in phase III clinical trials.

96-Week Aptivus Results

The 96-week follow-up data from the phase III studies of Aptivus were reported by Charles Farthing, MD, of the AIDS Healthcare Foundation in Los Angeles. The studies were RESIST 1 and RESIST 2, two ongoing phase III clinical trials involving patients who have tried and failed at least two PI-based regimens in the past. RESIST 1 is taking place in North America and Australia and RESIST 2 is being conducted in Europe and Latin America. All patients in the studies have been randomized to take an optimized background regimen (OBR) of standard HIV drugs plus Norvir® (ritonavir)-boosted Aptivus or a Norvir-boosted comparator PI.

A total of 1,509 patients were enrolled into the studies. Forty-eight week study data reported previously found that Aptivus was superior to comparator PIs, especially when combined with other HIV drugs that patients' viruses are sensitive to.

After 96 weeks of treatment, patients in the Aptivus groups were twice as likely to have a viral load that was at least 1 log below their pre-RESIST levels. This viral load benefit was seen in 26.4% of patients in the Aptivus groups, compared to 10.7% of patients in the comparator PI groups. The benefit was most pronounced in patients who incorporated Fuzeon® (enfuvirtide) into their drug regimen – most patients had not used this drug prior to enrolling in RESIST – with 45.2% in the Aptivus groups showing a 1 log reduction in viral load below their pre-RESIST levels, compared to 16.5% in the comparator PI groups.

Approximately 20% of patients in the Aptivus groups had viral loads below 50 after 96 weeks, compared to 9.1% in the comparator PI groups.

In conclusion, Dr. Farthing and his fellow authors said that the 96-week results support the antiviral effectiveness of Norvir-boosted Aptivus in treatment-experienced patients.

Aptivus vs. Prezista

Both Aptivus and Prezista are approved for the treatment of HIV in people who have tried and failed other HIV medications – notably other PIs – in the past. Understandably, one of the most frequent questions facing HIV-positive today in need of one of these PIs is: which agent to use? While a head-to-head clinical trial comparing these two drugs has not been conducted, two British researchers decided to compare the results of each drug's phase III study results to draw some informal conclusions.

In this analysis, Andrew Hill, MD, of the University of Liverpool, and Graeme Moyle, MD, of Chelsea Westminster Hospital in London, compared the results of the Aptivus RESIST studies and the Prezista POWER studies. Like the RESIST studies reviewed above, the phase III POWER 1 and POWER 2 trials randomized highly treatment-experienced patients to OBR plus Norvir-boosted Prezista or a Norvir-boosted comparator PI.

As summarized by the study authors, the RESIST and POWER studies were very similar in terms of average age, gender, race, pre-study viral loads and CD4 cell counts, prior treatment experience, and evidence of drug resistance. There were, however, a few key differences. For starters, there were considerably fewer people enrolled in the POWER studies compared to the RESIST studies (255 vs. 1,509 patients, respectively). Second, more people (23%) in POWER used "double-boosted" comparator PIs – two full-dose PIs combined with Norvir – compared to zero patients in the RESIST studies. Third, Fuzeon was more likely to be used in POWER compared to RESIST (47% vs. 25%, respectively). And last, 17% of RESIST patients had virus sensitive to non-nucleoside reverse transcriptase inhibitors (NNRTIs) and used one of the available options, compared to POWER, in which NNRTI use was not allowed. These differences do prevent a clear and concise comparison of the results.

After 48 weeks of treatment in both studies, the benefit of Norvir-boosted Prezista over the comparator PIs in POWER was greater than the benefit of Norvir-boosted Aptivus over the comparator PIs in RESIST. Approximately 46% in the Prezista POWER groups had viral loads below 50, compared to 10% in the comparator PI POWER groups. Conversely, in the RESIST studies, 23% of patients in the Aptivus groups had viral loads below 50 after 48 weeks, compared to 10% of patients in the comparator PI groups.

CD4 (T4) cell count gains were also more pronounced among those in POWER compared to RESIST. Patients in the Prezista groups had 83 more CD4 cells than those taking comparator PIs after 48 weeks, whereas patients in the Aptivus groups had 24 more CD4 cells than those taking comparator PIs.

While the addition of Fuzeon has been said to be a major factor associated with the success of these PIs in treatment-experienced patients, Drs. Hill and Moyle pointed out that Prezista showed higher effectiveness than Aptivus, when compared to comparator PIs, regardless of Fuzeon use.

In conclusion, the authors indicated that despite the limitations of such an informal comparison of study results, Prezista likely has efficacy advantages over Aptivus in terms of managing drug-resistant HIV.

PI History and Responses to Prezista

While the POWER studies have demonstrated that Prezista is a useful option in patients who have failed other PIs in the past, data are still being generated to determine how well Prezista works against HIV that has been previously treated with specific PI options. A study reported at ICAAC by a team of Tibotec investigators provided some important information in this regard, notably for HIV-positive people who have used Kaletra® (lopinavir/ritonavir), Lexiva® (fosamprenavir), and Aptivus in the past.

The analysis included 131 patients participating in POWER 1 and POWER 2, along with 327 patients participating in POWER 3, a study that provided open-label "early access" to Prezista for people in need of new treatment options. Of the POWER 1 and 2 patients included, 75 had taken Kaletra before enrolling, 32 had taken Lexiva before enrolling, and none had taken Aptivus before enrolling (prior treatment with Aptivus wasn't allowed in these two studies). In POWER 3, 117 had prior Kaletra experience, 42 had prior Lexiva experience, and 51 had prior Aptivus experience.

After 24 weeks of treatment, approximately 67% of all patients had viral loads that were at least 1 log below their pre-POWER levels, regardless of their past experience with Kaletra, Lexiva, or Aptivus. Among those who had used Aptivus in the past, the average viral load drop 24 weeks into the POWER studies was 1.64 log. Among those who had used Kaletra or Lexiva in the past, the respective viral load drops were 1.72 and 1.66 log after 24 weeks of Aptivus treatment. There were no statistical differences between these three groups, meaning that Norvir-boosted Prezista seemed to work well among the patients, regardless of which PI that had used in the past.

The researchers also noted that after 24 weeks of Aptivus treatment, between 40% and 44% of patients who had failed an Aptivus-, Kaletra-, or Lexiva-based regimen had viral loads below 50.

Considering that Aptivus has been labeled a "last hope" PI option for people who have tried and failed other PIs, it appears that Prezista – with its activity in patients no longer responding to Aptivus – offers an advantage to those truly at the end of their treatment rope.

Sources:

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Hill A, Moyle G. Relative week 48 antiviral efficacy of TMC114/r and tipranavir/r versus control PI in the POWER and RESIST trials [Abstract H-1386]. 46th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, 2006.
