Long-Term Efficacy and Safety of Tipranavir Boosted With Ritonavir

January 18, 2008
By Kirk M. Chan-Tack, MD [1], Jeffrey S. Murray, MD [2], and Debra B. Birnkrant, MD [3]

Critical Views in Infectious Disease Medicine A
Whenever possible, the results from a study should be discussed in the context of relevant data from other sources. Markowitz and colleagues recently reported 80-week results of study BI 1182.2, an open-label, randomized, multicenter, phase 2 study that evaluated the safety and efficacy of 2 doses of tipranavir/ritonavir (TPV/r) in combination with a nucleoside reverse transcriptase inhibitor (NRTI) and a nonnucleoside reverse transcriptase inhibitor (NNRTI) in 41 patients with HIV-1 infection who experienced treatment failure with 2 or more protease inhibitor (PI)-based regimens. Eligible patients were NNRTI-naive and had at least 1 NRTI available, determined by genotypic resistance testing. In this pilot study, 19 patients received TPV/r 500/100 mg bid and 22 patients received TPV/r 1000/100 mg bid. Clinically significant toxicities included grade 3/4 elevations in alanine aminotransferase (ALT) and triglyceride levels. The study data suggested that ALT increases were TPV dose-dependent.

The applicability of the study results for clinical practice is questionable for several reasons. First, neither of the dosages in study BI 1182.2 is approved in the tipranavir labeling. Second, this phase 2 study did not include a control arm and was underpowered to distinguish efficacy differences between doses. Third, all patients in this study had exposure to at least 3 fully active antiretroviral drugs. In contrast, patients in the pivotal phase 3 studies had triple-class experience (NRTI, NNRTI, PI) and previous exposure to a median of 6 NRTIs, 1 NNRTI, and 4 PIs. Fourth, the authors seem to minimize discussion about TPV/r and drug interactions. TPV/r has an extensive and complex drug-interaction profile, and the ability to predict anticipated interactions with other drugs can be challenging. The potential for interactions to occur when TPV/r is co-administered with other drugs should be considered before and during TPV/r use. Larger studies have generated substantial amounts of data on the safety, tolerability, pharmacokinetics, and efficacy of TPV/r. The phase 2 dose-finding study (BI 1182.52) was a 24-week, multicenter, double-blind, randomized trial that evaluated the safety, pharmacokinetics, and efficacy of 3 doses of TPV/r in HIV-1-infected patients.
patients with triple-drug class experience, including at least 2 PI-based regimens. A total of 216 patients were randomly selected to receive TPV/r 500/100 mg bid (n = 73), TPV/r 500/200 mg bid (n = 72), or TPV/r 750/200 mg bid (n = 71). This study provided further evidence that increases in ALT levels were TPV dose-dependent. At week 24, the proportion of patients with grade 3/4 elevations in ALT levels in the 3 treatment arms (TPV/r 500/100 mg bid, TPV/r 500/200 mg bid, and TPV/r 750/200 mg bid) was 5.5%, 11.1%, and 21.1%, respectively.3

TPV and ritonavir (RTV) exposure data analysis suggested that these ALT level increases were associated with increased TPV exposures and not RTV exposures.4 Study BI 1182.52 also demonstrated increased rates of hypertriglyceridemia with TPV/r. At week 24, the proportion of patients with grade 3/4 elevations in triglyceride levels in the 3 treatment arms (TPV/r 500/100 mg bid, TPV/r 500/200 mg bid, and TPV/r 750/200 mg bid) was 16.4%, 27.8%, and 22.5%, respectively. Another important safety finding in the study was that the highest rate of grade 3/4 laboratory abnormalities and study discontinuations because of adverse events occurred in the group assigned to receive TPV/r 750/200 mg bid.3

TPV/r 500/200 mg bid was selected for the phase 3 studies based on the safety, efficacy, and pharmacokinetic data from study BI 1182.525,6 and was subsequently approved for combination antiretroviral treatment of HIV-1-infected adults with evidence of viral replication who are highly treatment-experienced or have HIV-1 strains resistant to multiple PIs.2 Forty-eight week data from the phase 3 studies were published,7 and the tipranavir labeling was recently updated with this data through the traditional approval process.8

Of note, TPV/r is not indicated for treatment-naive HIV-infected patients.8 Study BI 1182.33 was a phase 2b/3, multicenter, randomized, open-label, active controlled trial that compared the safety and efficacy of TPV 500 mg bid and RTV 100 mg bid or 200 mg bid in combination with a standard background regimen (tenofovir 300 mg qd and lamivudine 300 mg qd) with that of lopinavir/ritonavir (LPV/r) 400/100 mg bid and a standard background regimen (tenofovir 300 mg qd and lamivudine 300 mg qd) in treatment-naive HIV-1-infected adults for 48 weeks, with extension up to 156 weeks. A total of 562 patients were randomly selected to receive TPV/r 500/100 mg bid (n = 187), TPV/r 500/200 mg bid (n = 186), or LPV/r 400/100 mg bid (n = 185).9 Forty-eight week data from the study showed a higher rate of grade 3/4 elevations in ALT levels in the TPV/r 500/200 mg bid group (19.6%) than in the TPV/r 500/100 mg bid group (6.0%) and the LPV/r 400/100 mg bid group (3.8%).9

Because of these safety concerns, the data safety monitoring board (DSMB) recommended closure of the 500/200 mg bid arm in February 2006.10 The DSMB and the agent’s manufacturer and clinical trial sponsor, Boehringer Ingelheim, supported continuation of the TPV/r 500/100 mg bid and LPV/r 400/100 mg bid groups. However, the results of a post hoc week 48 efficacy analysis performed after all patients had completed the week 60 visit revealed that TPV/r 500/100 mg bid was no longer noninferior to LPV/r. The study authors concluded that TPV/r cannot be recommended for treatment-naive HIV-infected patients at the doses evaluated in study BI 1182.33.9 Based on these findings, the study was formally closed by Boehringer Ingelheim in June 2006.11

We hope the complete results of study BI 1182.33 will be published in a peer-reviewed journal in an effort to provide health care providers, patients, and HIV experts access to data from this important multicenter, randomized, controlled clinical trial. Academicians, investigators, and pharmaceutical sponsors are encouraged to provide balance when publishing results of studies during all phases of drug development. Careful, thorough discussion of the strengths and weaknesses of a study could substantially increase the value of scientific communication. This approach may foster additional clinical, scientific, and regulatory discussions, as well as increase the level of transparency throughout the drug development process.

References:

4. Center for Drug Evaluation and Research Approval Package for Tipranavir (NDA 21-814,


Source URL:

Links: