Boosting HIV Treatment Options: Good News, New Challenges

Pedro Cahn and Omar Sued
Fundación Huésped, Buenos Aires, Argentina

(See the major article by Gallant et al on pages 32–9.)

Keywords. pharmacoenhancer; cobicistat; boosted PIs.

For >15 years, ritonavir (RTV) has been the only pharmacokinetic enhancer (ie, booster) for human immunodeficiency virus (HIV) protease inhibitors. The development of cobicistat (COBI) promises to provide an alternative to RTV without direct antiviral effects of its own. COBI, a potent cytochrome P450 3A (CYP3A) inhibitor recently approved by the Food and Drug Administration (FDA) for use in a single-tablet regimen of elvitegravir/COBI/emtricitabine(FTC)/tenofovir disoproxil fumarate (TDF), is currently being studied in phase 3 trials as booster of other antiretroviral drugs. In vitro studies demonstrate that COBI, unlike RTV, is a weak inhibitor for CYP2D6 and does not have inhibitory effects on other CYP isoforms (ie, CYP1A2, CYP2C09, and CYP2C19), making pharmacologic interactions more predictable [1]. COBI also seems to have less impact than RTV on normal adipocyte functions, such as lipid accumulation and/or response to insulin, which may offer the potential for fewer adverse biochemical effects relative to RTV [2]. In addition, the better solubility of COBI allows creation of a tablet formulation and coformulations that might foster the availability of other single-tablet regimens.

In this issue of the Journal, Gallant et al report the 48-week results of a study comparing COBI with RTV as a pharmacoenhancer for atazanavir (ATV) plus FTC/TDF in 698 treatment-naive HIV type 1 (HIV-1)–infected patients. Study subjects were recruited in the United States, the Dominican Republic, Mexico, Thailand, Portugal, Germany, the United Kingdom, Italy, and Switzerland and were randomly assigned in a 1:1 ratio to receive COBI or RTV. Most of the participants (60%) were white, and similar to other large trials, the proportion of women (17%) was low. Twenty-four percent reported Hispanic/Latino ethnicity. The study allowed the inclusion of individuals with active hepatitis, with hepatitis B present in 3.6% of patients and hepatitis C in 5.3%. The immunologic status of the patients was relatively good, with 48% having CD4+ T-cell count of >350 cells/mL, reflecting the latest recommendations for treatment initiation [3]. Randomization was stratified by viral load, with 39.7% of patients having >100 000 HIV RNA copies/mL at baseline. Of the 692 patients who initiated treatment with the study medication, 344 were in the COBI arm and 348 were in the RTV arm. At 48 weeks, COBI-boosted ATV was shown to be virologically noninferior to RTV-boosted ATV, with 293 patients (85.2%) and 304 patients (87.4%) in the COBI and RTV arms, respectively, achieving an HIV-1 RNA load of <50 copies/mL, in accordance with the FDA snapshot intention-to-treat analysis (observed difference, −2.2% [95% confidence interval, −7.4% to 3.0%]). Mean increases in CD4+ T-cell counts were also similar in the COBI and RTV groups (+213 cells/mm³ and +219 cells/mm³, respectively at week 48). Favorable responses were comparable in patients with a high viral load (86.4% in the COBI group vs 86.0% in the RTV group). Of the 95 subjects who were not reported as having virologic success, treatment in 34 was defined as virologic failure (5.8% and 4% in the COBI and RTV arms, respectively), but this small difference was not statistically significant. The remaining 61 patients discontinued the protocol because of adverse events or other reasons, despite having undetectable viral loads. No major tolerability issues were reported. Gastrointestinal adverse events were not statistically different between the COBI and RTV groups, with similar rates of nausea (17.7% and 16.4%, respectively), vomiting (7.3% and 4.6%, respectively), or diarrhea (15.4% and...
20.4%, respectively), but only 2 patients (1 in each arm) had to stop treatment because of gastrointestinal complaints. A similar tolerability profile was shown in another study comparing elvitegravir/COBI/FTC/TFV with COBI-boosted ATV [4]. The most common adverse events were those related to an elevated bilirubin level, a well-known side effect of ATV use, and included jaundice and scleral icterus, reaching rates of 40.7% and 36.2% in the COBI and RTV groups, respectively, although these rarely led to treatment discontinuation (3.5% in the COBI arm and 3.2% in the RTV group). A small increase in serum creatinine level, usually within the first 8 weeks of treatment, was observed in both arms (median change from baseline, +0.13 mg/dL vs +0.09 mg/dL; P < .001) with a concomitant decrease in the estimated glomerular filtration rate (eGFR; median change, −12.9 mL/min vs −9.1 mL/min; P < .001), although renal adverse events leading to treatment discontinuation were rarely reported. Only 6 patients (1.7%) in the COBI arm and 5 patients (1.4%) in the RTV group stopped receiving study drugs, and no patient required dialysis. Of note, in the COBI arm most of the patients (5 of 6) who stopped treatment had laboratory findings consistent with proximal tubulopathy, such as hypophosphatemia, proteinuria, or normoglycemic glycosuria, that resolved or improved after treatment discontinuation, whereas in the RTV group most of the patients (3 of 5) who stopped treatment showed an increase in their serum creatinine level without evidence of tubular dysfunction.

Renal safety emerged as a potential concern early in the development of COBI, as increases in the serum creatinine level were observed in patients treated with COBI-containing regimens. This increase is not associated with an actual decrease in the actual GFR; instead, COBI drives a reduction in the eGFR, because of an inhibition of the secretion of creatinine, without affecting the actual GFR [5]. An increase of ≥0.4 mg/dL from baseline was proposed for distinguishing the effect of cobicistat on the serum creatinine level from genuine renal dysfunction [6]. In the study by Gallant et al, changes in renal measurements were observed in both groups, and abnormalities reverted after discontinuation of study drugs. It has been previously reported that TDF, which was used in both study arms, can cause proximal tubulopathy [7]. Observational studies have also shown that this toxicity might be more frequent when TDF is associated with ritonavir-boosted protease inhibitors [8]. Experiments in vitro [9] have shown that COBI increases the intestinal absorption of protease inhibitors and TDF. The clinical relevance of these findings remains unclear and deserves further research. Of note, although the number of patients who discontinued participation in this phase 3 study because of renal events was small, proximal tubulopathy features were observed in 5 of 6 subjects in the COBI arm and in 2 of 5 subjects in the RTV arm. During COBI use, routine renal monitoring (eg, urine protein level, urine glucose level, serum creatinine level, and calculated creatinine clearance rate) every 6 months (as recommended for patients receiving TDF) is advised for early identification of tubulopathy. A tenofovir prodrug in development, tenofovir alafenamide fumarate (TAF), formerly known as GS-7340, has antiviral potency similar to or exceeding that of TDF. It was designed to reach higher concentrations in cells and lymphoid tissues, with lower levels in blood serum, which may minimize its detrimental effects on kidneys and bones [10]. Studies to evaluate the efficacy of TAF in a tablet coformulated with elvitegravir/COBI and FTC are underway [11]. How this new drug will interact with COBI remains a research question.

The results of the study by Gallant et al validate those reported by Elion et al in the phase 2 study of COBI versus RIT [12]. In that study, 89 patients were randomly assigned in a 2:1 ratio to the ATV/COBI arm. Through week 48, both groups achieved and maintained similar rates of virologic suppression and similar CD4+ T-cell count increases. Similarly, the most common toxicity was also driven by high bilirubin levels. Actually, slightly higher bilirubin levels in the COBI arm were found in the studies by Elion et al and Gallant et al; it was hypothesized that differences between COBI and RTV in the affinity for off-target metabolic enzymes could be implicated, although levels of ATV measured in a subsample of patients were not significantly different between arms. Gilead has submitted a New Drug Application to the FDA for marketing approval of cobicistat as a boosting agent for darunavir and ATV [13]. Studies of coformulations with these drugs are ongoing [14]. Of note, Gilead, the COBI patent holder, signed an agreement with the Medicines Patent Pool to transfer the manufacturing technology to Indian companies in order to produce generic versions of this drug, making it potentially available in 102 low- and middle-income countries [15].

In conclusion, this phase 3 study shows that COBI-boosted ATV has high efficacy, a good tolerability profile, and is noninferior to RTV-boosted ATV. Its potential role in novel ART combinations will depend on the confirmation of its promising data as a new boosting agent, cost comparisons to ritonavir, and the availability of new coformulations. HIV caregivers now have a new tool for managing their patients, as well as a new challenge in understanding the implications of changes in results of renal function tests.

Note

Potential conflicts of interest. P. C. is a member of the WHO Guidelines Panel and the IAS-USA Guidelines Panel; he has served on advisory boards for GlaxoSmithKline (ViiV), Merck, Pfizer, Gilead Sciences, and Tibotec (Janssen) Therapeutics; he has been an investigator for Abbott; Aventis, Boehringer Ingelheim Pharmaceuticals, Gilead Sciences, GlaxoSmithKline, Merck, Pfizer, Pharmasset, Roche Laboratories, and Tibotec Therapeutics; and his institution has received honoraria from Abbott Laboratories, Bristol-Myers Squibb, GlaxoSmithKline, Merck & Co, Inc,
Pfizer Inc, and Tibotec Therapeutics for speaking or chairing engagements he performed. O. S. certifies no potential conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References