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Atazanavir

A Viewpoint by Peter J. Piliero

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Atazanavir, formerly BMS-232632, is a novel azapeptide HIV-1 protease inhibitor currently in the final stages of clinical development. It has been shown in clinical trials to offer similar antiviral potency as nelfinavir, as measured by viral load reduction during two weeks of monotherapy. In addition, in phase II and phase III studies of combination antiretroviral therapy (ART) regimens given to antiretroviral-naive patients, atazanavir has been shown to have similar, albeit lower than expected, efficacy relative to nelfinavir- and efavirenz-based regimens. As there are already five marketed protease inhibitors, what does atazanavir offer to the clinician treating HIV-infected patients?

Atazanavir is the first non ritonavir-boosted protease inhibitor that can be administered once daily (two capsules with food). Strict adherence to antiretroviral therapy has been shown to be associated with a greater likelihood of durable viral suppression. As such, atazanavir offers a convenient administration schedule with a low pill burden that should enhance adherence.

Tolerability of ART regimens has also been shown to be associated with likelihood to adhere to therapy. Clinical trials have proven atazanavir to be a well-tolerated agent with the most common toxicity being unconjugated hyperbilirubinaemia that infrequently led to discontinuation of therapy. In addition to acute medication tolerability, with prolonged ART potentially serious long-term toxicities, including hyperlipidaemia, insulin resistance and lipodystrophy, have been identified. All of the currently available protease inhibitors have been associated with the development of hyperlipidaemia. This occurs infrequently with atazanavir. The implication of such a favourable lipid profile would be reduced cardiovascular toxicity compared with the other protease inhibitors. As well, insulin resistance and lipodystrophy have occurred infrequently in clinical trials of atazanavir.

Resistance to antiretroviral agents is increasing in prevalence in areas of the world that have access to treatment. In *in vitro* studies, resistance to atazanavir was commonly seen in viral isolates with resistance to more than two of the currently available protease inhibitors. In contrast, antiretroviral-naive patients who failed an atazanavir-containing regimen usually developed a genotypic mutation that conferred resistance to atazanavir while maintaining sensitivity to the other protease inhibitors.

Synthesizing all of the data on atazanavir available to date, it would seem that atazanavir is likely to be most useful in patients who are antiretroviral- or protease inhibitor-naive. It would provide for a simple, convenient, and well-tolerated protease inhibitor to be combined with two standard reverse transcriptase inhibitors. However, with ritonavir-boosted protease inhibitor-based therapy now clearly shown to produce more durable virologic suppression than non-boosted protease inhibitor-based therapy in antiretroviral-naive patients, direct comparison of atazanavir to a ritonavir-boosted protease inhibitor-containing regimen would help define the comparability and differences of these alternative approaches. ▲