Substitution of protease inhibitors during treatment of patients with human immunodeficiency virus infection: frequency, mode, reasons and mid-term outcome

J Antimicrob Chemother 2000; 45: 261–263
Roberto M anfredi* and Francesco Chiodo

Department of Clinical and Experimental Medicine, Division of Infectious Diseases, University of Bologna, S. O rsola Hospital, Via M assarenti 11, I-40138 Bologna, Italy

*Corresponding author. Tel: +39-051-63-63-355; Fax: +39-051-34-35-00.

Sir,

Protease inhibitors (PIs) have been available for the treatment of patients infected with the human immunodeficiency virus (HIV) for 3 years, but the emergence of resistant strains and the toxicity associated with highly active antiretroviral therapy (HAART) have meant that PIs have increasingly been substituted with alternative drugs belonging to this group. Since very limited data are currently available in the literature regarding the implications to current clinical practice of substituting one PI with another, a retrospective survey of the clinical and laboratory records of 908 consecutive patients treated with these drugs since June 1996 was undertaken in order to determine the reasons for, frequency of and outcome associated with this therapeutic measure.

PI-containing antiretroviral regimens were administered according to yearly revised international guidelines and included indinavir, ritonavir or saquinavir (hard-gelatin capsules) since the summer of 1996 and nelfinavir since late summer 1998. A treatment substitution on the grounds of poor efficacy was prompted by one or more of the following: <1 log_{10} decrease in the plasma viral load compared with the baseline value (i.e. before treatment with a PI was initiated); ≥ 0.7 log_{10} rebound of the plasma HIV RNA concentration after reaching an undetectable level; a viral load persistently > 5 × 10^2 copies/L together with a decline in the CD4 + lymphocyte count of ≥ 20% or ≥ 150 × 10^6 cells/L compared with the baseline value; or a CD4 + count persistently < 100 × 10^6 cells/L. All of these variables were measured on two or more occasions after > 6 months of therapy. Alternatively, a substitution related to poor tolerability or toxicity was based on the presence of clinical signs and/or symptoms and laboratory investigations consistent with adverse events or toxicity. The response to treatment with the new regimen was assessed 9 months after modification and classified as favourable according to the following criteria: ≥ 1 log_{10} reduction in the plasma viral load compared with the value at the time of treatment modification, or achieving viral suppression, together with an increase in the CD4 + cell count of ≥ 15% or ≥ 100 × 10^6 cells/L compared with the value at the time of treatment modification, in patients who had failed to respond to treatment; or tolerance of the treatment regimen when intolerability was the reason for the substitution.

During the 3 year study period there were 252 substitutions of PIs in 205 patients (Table). Substitutions of ritonavir occurred more frequently than those of saquinavir (P < 0.0001) and substitutions of saquinavir occurred more frequently than those of indinavir (P < 0.0002). One hundred and thirty-six (54%) substitutions were made because of poor tolerability, ritonavir and indinavir being tolerated less well than saquinavir (P < 0.0001); 83.8% of patients benefited from these substitutions. A switch made on the grounds of treatment failure was observed significantly more frequently in patients receiving saquinavir than in those given either ritonavir or indinavir (P < 0.0001). Indinavir and ritonavir proved to be effective for longer periods than saquinavir (P < 0.0001), but the likelihood of patients’ conditions improving in the 9 months following a substitution of indinavir or ritonavir with another PI was significantly lower than when saquinavir was similarly substituted (P < 0.0005). Significant improvements in virological and immunological variables were noted in only 14/50 (28%) patients who were switched to alternative PIs after failing to respond to regimens containing ritonavir or indinavir, compared with 51/66 (77.3%) patients whose regimens were modified because of failure to respond to saquinavir (P < 0.0001) (Table).

Substitutions of PIs administered as components of therapeutic regimens to patients with HIV infections are expected to occur with increasing frequency and intense efforts are currently being made to identify salvage regimens capable of achieving (or maintaining) viral suppression following failure of or intolerance to HAART. Investigators who carried out an earlier study in Italy reported that advanced HIV disease at baseline and poor compliance with HAART were predictive of failure in 250 patients who had received PI-containing regimens and who were followed up for a median of 8 months; the administration of saquinavir was independently related to virological failure, compared with HAART regimens that included...
Correspondence

indinavir or ritonavir. In a subsequent study, Wit et al. followed 271 patients for 48 weeks after the initiation of HAART. They identified a high baseline plasma viral load and a low baseline CD4+ lymphocyte count, as well as the administration of saquinavir (as opposed to other PIs), as risk factors for treatment failure. They also observed that substitutions of PIs because of intolerance occurred more frequently in patients receiving ritonavir-containing regimens than in those treated with regimens containing other PIs. It has been demonstrated, however, that a broad range of variables can interfere with the subsequent response to salvage HAART.

In our experience the reduced efficacy of saquinavir was associated with a better safety profile and a better short-term outcome following PI substitution, whereas the potent and sustained activities of ritonavir and indinavir were undermined by high rates of adverse events and less favourable outcomes after substitution. We believe that controlled clinical trials should be undertaken to compare an aggressive therapeutic strategy, based on the early administration of the most potent compounds available, with a conservative option comprising initial treatment with less effective, but better tolerated drugs which may be associated with greater risks of disease progression and the selection of resistant strains. Since each antiretroviral agent has its own therapeutic niche, the risks and benefits should be monitored according to clinical and laboratory criteria during a prolonged follow-up period.

References


Correspondence


