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Amprenavir
A Viewpoint by Graeme Moyle

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Although the availability of HIV protease inhibitors represents a major improvement in the management of HIV infection, it is increasingly recognised that many patients commencing triple combination antiretroviral therapy including a protease inhibitor fail to achieve the optimal virological response i.e. a viral load below the detection limits of a sensitive viral load assay. Additionally, many patients who initially achieve an optimal response to therapy fail to sustain an undetectable viral load for prolonged periods. Adherence to therapy appears to be critical to treatment response. However, 3 of the 4 approved protease inhibitors require 3-times-daily administration (although twice-daily administration is under investigation) and the ingestion of large numbers of tablets, and optimal administration of these agents often involves certain food restrictions; ultimately, all these factors may challenge the patient's ability to adhere to treatment.

Continued viral replication in the presence of the selective pressure of an antiviral agent leads to the selection of viral variants with reduced sensitivity or resistance to the drug. The development of resistance to one of the available protease inhibitors may also unfavourably influence sensitivity to other members of the therapeutic class. Thus, the ideal characteristics of a new protease inhibitor should include the following:

- activity similar to or better than that of available agents
- once- or twice-daily administration without food restrictions
- activity against virus resistant to current agents
- a resistance profile which does not limit the activity of other protease inhibitors.

Initial data from small studies with amprenavir suggest that this agent may possess some of these ideal characteristics.

Amprenavir has shown activity comparable with that of other protease inhibitors and studies directly comparing amprenavir with other agents are now underway. The drug can be administered twice daily; however, food appears to affect the absorption of amprenavir and may necessitate administration of the drug under fasting conditions. The adverse events reported thus far with amprenavir appear generally mild and manageable. Long term adverse events such as diabetes mellitus and lipodystrophy were not reported with approved protease inhibitors until after commercialisation and require further characterisation. Physicians and patients will watch with interest to see if these adverse effects are also observed during therapy with amprenavir.

Data from Merck suggest that indinavir may select for HIV which is resistant to multiple protease inhibitors including amprenavir.[1] It is also likely that this will be the case with other approved protease inhibitors. *In vitro* selection studies with amprenavir suggest that a mutation at codon 50 is critical in the genesis of resistance to this compound. Initial variants selected by amprenavir lead to small (2- to 5-fold) improvements in sensitivity to saquinavir and indinavir. Although mutants with a single mutation at codon 50 showed significant growth impairment, a triple mutant containing mutant codons 46, 47 and 50 selected for by continued passage, showed similar growth rates to wild-type. Passage of the triple mutant with indinavir selected a mutant with 10- to 20-fold resistance to both drugs. However, interestingly, passage of this triple mutant in the presence of increasing concentrations of saquinavir lead to the development of saquinavir resistance but resensitisation to amprenavir.[2-4] It remains to be seen whether this phenomenon can be reproduced *in vivo*. In many cases, cross-resistance between protease inhibitors appears to be related to the number of accumulated mutations in the protease gene,[5] hence it is likely that amprenavir will eventually select for virus resistant to other protease inhibitors. However, it may be possible that some patients will benefit from a second protease inhibitor if therapy is promptly switched before multiple mutations have accumulated.

Drug interactions with other agents metabolised by cytochrome P450 3A4 will occur with amprenavir and interactions with other protease inhibitors may lead to higher levels of one or both agents. Increasingly, dual protease inhibitor therapy is used both in salvage regimens and in patients at risk of not achieving an optimal response to standard triple therapy. Amprenavir appears to be a good candidate for combination use and studies are currently examining this issue.

Therefore, initial data suggest that amprenavir is an active, generally well tolerated protease inhibitor with a potentially valuable role in a number of clinical scenarios. ▲

References

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