BOOSTING PROTEASE INHIBITORS WITH LOW-DOSE RITONAVIR – UNRAVELLING THE MYSTERY

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The advent of highly active antiretroviral treatment (HAART) has had the dramatic effect of changing HIV infection from a relentlessly progressive disease with inevitable death to a disease that is chronic and manageable. The goal of HAART is to suppress HIV replication maximally, and thereby restore immunological function, reduce HIV-related morbidity and mortality, and improve quality of life.[1] HIV-infected persons who qualify for treatment can be treated with a HAART regimen consisting of two nucleoside reverse transcriptase inhibitors (NRTIs) combined with a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI).[2]

In the presence of subtherapeutic drug levels, viral replication persists, resulting in the formation of mutations and resistant variants.[3] There are various reasons for failure to suppress viral replication to undetectable levels.[4] Non-adherence is one of the major reasons for incomplete suppression.[3] Non-adherence can be due to high pill burden, high frequency of dosing, dietary restrictions, and lack of tolerance of adverse effects.[4]

Pharmacological factors also play an important role in treatment failure. Pharmacodynamic drug-drug interactions can change the pharmacological effect of a drug. The pharmacological effect of two or more drugs can act additively or antagonistically.[4] Pharmacokinetic drug-drug interactions are associated with inappropriate plasma concentration of drugs. Changes in plasma concentration of drugs can be the result of inadequate absorption, inadequate transport, inadequate metabolism, or inadequate elimination.[4]

Antiretroviral drugs and antibiotics used for opportunistic infections are metabolised by various isoenzymes in the cytochrome P450 (CYP) enzyme system, which consists of a superfamily of haemoproteins.[4] These isoenzymes catalyse the oxidative metabolism of a wide variety of exogenous chemicals such as therapeutic drugs, carcinogens and toxins; and endogenous compounds such as steroids, fatty acids and prostaglandins.[5] The CYP enzyme family plays an important role in phase 1 metabolism of these drugs.[5] The biotransformation of these drugs and chemicals is responsible for the clinically significant drug interactions during multiple drug therapy.[6] Each isoenzyme of the CYP family is a specific gene product with characteristic substrate specificity.[5] Although there are many types of isoenzymes, only six isoenzymes, namely CYP3A4, 1A2, 2C9, 2C19, 2D6 and 2E1, are important in the hepatic metabolism of the drugs. Many drug interactions are the result of either induction or inhibition of the CYP isoenzymes.[7] CYP3A4 is the most predominant isoenzyme in the liver, accounting for 30% of CYP proteins in the liver, and metabolising 30 - 40% of drugs, including the PIs and the NNRTIs.[7] Substantial levels of CYP3A4 are also present in the small-intestinal epithelium, and play a role in the presystemic elimination of orally administered drugs.[7]

Another protein, the P-glycoprotein, plays an important role in actual body and tissue sanctuary site penetration and this remains important for the oral bioavailability of certain drugs.[8]

ENZYME INHIBITION

The majority of clinically important drug interactions are based on inhibition of the CYP isoenzymes, thus causing a decreased metabolism of medications. A drug may inhibit a CYP isoenzyme whether it is a substrate of that isoenzyme or not.[6] Inhibition of CYP isoenzymes causes a dose-related increase in plasma concentration of substrate within minutes to hours of the first dose, thus potentially causing toxicity.[4] Drugs with a long half-life and a narrow therapeutic index can potentially cause serious side-effects.[4]

For the sake of completion enzyme inducers increase the production of CYP isoenzymes, and thus accelerate the metabolism of various medications. It is worth noting that the antiretroviral drug efavirenz is both an inducer and an inhibitor of CYP isoenzymes.[4]

RITONAVIR-BOOSTING EFFECT ON PIs

HAART regimens that include a PI have had a dramatic impact on HIV-related morbidity and mortality. Following their

introduction into clinical practice, there has been a sharp decline in AIDS-related deaths by 47% in the USA.[9] However, the limited bioavailability of, and lack of adherence to, PIs because of high frequency of dosing, high pill burden, dietary and fluid restrictions and intolerance of adverse effects, can lead to the development of resistant strains and virological failure.[10] Any strategies that reduce the collective impact of the adherence–limiting factors mentioned above will improve the patient's motivation and willingness to adhere to therapy.[11] In this section the authors will limit the PI drugs to those currently and readily available in South Africa.

Some PIs (lopinavir and saquinavir) undergo extensive first-pass metabolism via the CYP isoenzyme system, primarily via CYP3A4 in the liver and the small intestine.[3] Of all the PIs, ritonavir is the most potent and most effective inhibitor of CYP3A4, and is therefore also a potent inhibitor of the metabolism of the other PIs.[3] Ritonavir also inhibits CYP3A4 in areas of the body outside the liver and the intestinal tract.[12]

Co-administration (boosting) of a PI with low-dose ritonavir (100 - 200 mg) can increase the total area under the concentration versus time curve (AUC) of the primary PI, as well as the minimum concentration (C_{min}). The maximum concentration (C_{max}) of the primary PI is also increased, although to a lesser extent than that for AUC and C_{min}.[3] Plasma peak and trough levels of the primary PI in a boosted PI regimen is generally higher than when the primary PI is given without boosting with ritonavir. The antiretroviral activity of the primary PI is consequently enhanced in terms of intensity and duration.[12] The pharmacokinetics of the different PIs varies, as does the effect ritonavir has on their pharmacokinetics.[13]

Two distinct patterns of PI boosting are seen, namely

- the C_{max} boosting effect with a modest $t_{1/2}$ boosting, or
- the $t_{1/2}$ boosting with a modest AUC level boosting.[13]

Table I divides the relevant PIs into C_{max} and $t_{1/2}$ boosting patterns.

TABLE I. TWO DISTINCT PATTERNS OF PI BOOSTING ARE PRESENT AND THE PHARMACOKINETICS OF THE RELEVANT PIs ARE DIVIDED BELOW

C_{max} boosting	$t_{1/2}$ boosting
Saquinavir	Amprenavir
Lopinavir	Indinavir
Nelfinavir – effect unknown	

Saquinavir is removed by first-pass metabolism in the small intestine, limiting its bioavailability. Ritonavir improves the efficacy of saquinavir by inhibiting first-pass metabolism and thereby increasing AUC, C_{min}, and C_{max}.[14] Indinavir has relatively good bioavailability, but has a comparatively short $t_{1/2}$. Ritonavir improves indinavir efficacy primarily by inhibiting hepatic metabolism, and decreasing systemic clearance.[15] This leads to larger increases in C_{min} than AUC, while having less effect on C_{max}.[16] Trough indinavir levels are maintained above the IC_{95}.[17] The effect of ritonavir boosting on nelfinavir pharmacokinetics is less than on other PIs, as nelfinavir is metabolised by several CYP isoenzymes, and has relatively good bioavailability.[18] Larger increases are observed in the AUC, C_{min} and C_{max} of nelfinavir's M8 metabolite, but the increases are generally no larger than 1-fold.[13] Lopinavir is only available in combination with ritonavir, and, like saquinavir, benefits from ritonavir's inhibition of first-pass intestinal metabolism.[13] Ritonavir's effect on amprenavir appears to be similar to its effect on indinavir, with inhibition of hepatic metabolism leading to larger increases in C_{min} than AUC.[16]

Low plasma levels of PIs are strongly related to virological failure, but it is ultimately the amount of free drug within the HIV-infected cell, where HIV replication actually occurs, that will most closely influence antiretroviral activity.[17] Drug efflux transporters play an important role in establishing and maintaining HIV sanctuary sites by lowering the intracellular drug concentrations via an efflux mechanism.[18-20] P-glycoprotein and multidrug-resistant protein (MRP) are two such drug efflux transporters whose substrates include PIs and NNRTIs. High levels of expression of these proteins may be found in patients treated for HIV infection, thereby reducing drug absorption from the intestinal tract and enhancing drug elimination in bile and urine.[20-22] P-glycoprotein and MRP efflux transporters in the endothelial cells of the blood-brain barrier may also prevent the transport of PIs into the central nervous system.[20,21,23] Evidence has been presented that ritonavir inhibits functional activity of P-glycoprotein and MRP efflux transporters, allowing a second PI to pass through cellular boundaries.[16,23-25] Thus ritonavir inhibition of efflux transporters combined with the bioavailability of higher plasma levels of the primary PI, appears to facilitate PI penetration into the HIV sanctuaries.[15,16,21,26] The inhibition of P-glycoprotein and MRP by ritonavir not only helps retain PI levels intracellularly, but also increases the oral bioavailability, systemic exposure and central nervous system penetration of the primary PI and ultimately decreases the secretion of the circulating drug into the intestinal lumen.[17,18,27]

ADVANTAGES OF PI BOOSTING

INCREASED POTENCY AND EFFICACY

HAART regimens containing an unboosted PI result in trough drug levels that are likely to be only slightly higher than the 50% inhibitory concentration (IC_{50}).[3] However, boosting with low-dose ritonavir results in primary PI trough levels becoming substantially higher than the IC_{50} or IC_{95}.[3] The addition of low-dose ritonavir to amprenavir, fosamprenavir or indinavir produces substantial increases in C_{min} and AUC, with more moderate or minimal increases in C_{max}.[13] Low-dose ritonavir substantially increases C_{min}, C_{max} and AUC of both lopinavir and saquinavir.[28] However, there is little effect on nelfinavir pharmacokinetics.[13]

DECREASED RISK OF DRUG RESISTANCE

The high peak and trough levels of the primary PI that are achieved with low-dose ritonavir boosting exceed the IC_{50} and

IC_{95} so that there is a high genetic barrier against the development of resistance.

REGIMEN SIMPLIFICATION

PI boosting with low-dose ritonavir results in greater oral bioavailability and longer half-life of the primary PI. Patient adherence is promoted by less frequent dosing, a lower pill burden, and the elimination of food and fluid restrictions.[3]

BOOSTED PI REGIMEN IN TREATMENT-EXPERIENCED PATIENTS

Treatment-experienced patients can also benefit greatly from PI boosting. In patients in whom previous regimens have failed, adequate virological suppression afforded by PI boosting can delay the emergence of new viral mutations that confer further PI resistance and cross-resistance, thereby helping to preserve future treatment options.[3]

DISADVANTAGES OF PI BOOSTING

ADVERSE EFFECTS

As a result of the higher peak levels reached with PI boosting, an increased frequency of PI-related adverse effects has been observed.[3] Indinavir-associated **nephrolithiasis** in PI-boosted regimens may increase in incidence.[29]

Dyslipidaemia, with elevated levels of total cholesterol, low-density lipoprotein cholesterol or triglycerides, is a PI-related adverse effect that has to be monitored closely because of the increased cardiovascular risk.[30] Dyslipidaemia, in the form of increased triglycerides, appears to be more severe with ritonavir than with other PIs.[31] Elevated serum lipid levels have been observed when indinavir, lopinavir or saquanavir is boosted with low-dose ritonavir.[32-39] **Gastro-intestinal** side-effects are common, especially diarrhoea. PI boosting with ritonavir cannot be used in patients who are allergic to ritonavir.

DRUG-DRUG INTERACTIONS

Since all the available PIs are metabolised by, and are inhibitors of, CYP3A4, and since ritonavir is a particularly potent inhibitor, numerous drug interactions can potentially occur with an inducer, an inhibitor or a substrate of this isoenzyme.[40]

Ritonavir metabolism also involves the CYP2D6 and 1A2 isoenzymes, so that co-administration of drugs that are metabolised by these isoenzymes may result in altered drug activity.[3]

Ritonavir also inhibits, although to a lesser extent, CYP2C19, which is important in the metabolism of nelfinavir, and the metabolism of its active metabolite, M8.[13]

Further, ritonavir can induce some P450 isoenzymes and this inhibiting effect may in some instances help to overcome other drugs that interact by induction.[13]

THE FUTURE

In view of the pharmacokinetics of low-dose ritonavir-boosted PIs with high AUC, high trough and peak levels, high C_{min}, good bioavailability, and high genetic barrier to mutations and resistance, is it not an opportune time to have a paradigm shift from the traditional triple therapy consisting of a backbone of two NRTIs together with a NNRTI or a PI, to monotherapy with low-dose ritonavir-boosted PIs such as LPVr (Kaletra)?[41]

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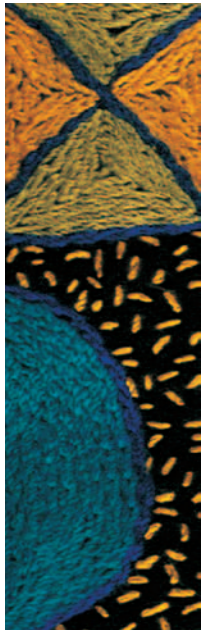

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