Research Review
PRODUCT REVIEW

Lopinavir/Ritonavir (Kaletra®)

About the Reviewer

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Abbreviations used in this review

CAD = coronary artery disease
GI = gastrointestinal
(HA)ART = (highly active) antiretroviral therapy
MI = myocardial infarction
(N)NRTI = (non-)nucleoside reverse transcriptase inhibitor
PI = protease inhibitor

This review discusses the evidence in support of the coformulated HIV-1 PI, lopinavir/ritonavir (Kaletra®). Since its approval in September 2000 in the US (April 2001 in Europe) for the treatment of HIV infection in adults and children aged >6 months, considerable experience has accumulated with lopinavir/ritonavir in both treatment-naïve and treatment-experienced patients.[1-3] Lopinavir/ritonavir is highly effective as a component of HAART regimens for HIV-1 infection; evidence also supports the use of lopinavir/ritonavir monotherapy as a therapeutic option in certain patients. In general, lopinavir/ritonavir is well tolerated and is characterised by a high genetic barrier to genotypic resistance, which helps to make this agent more forgiving of nonadherence than other PIs.

Kaletra® is an orally administered coformulated PI containing lopinavir and low-dose ritonavir that is indicated, in combination with other ART, for HIV-1 infection therapy in adults, adolescents and children.[1] Lopinavir/ritonavir is available in NZ as a tablet and an oral solution for patients with difficulty swallowing; it was previously available as a soft gel capsule.[4] Well-designed RCTs have shown that when used in combination with other ARTs, lopinavir/ritonavir provides durable virological suppression and improved immunological outcomes in both ART-naive and -experienced HIV-infected adults with virological failure. Furthermore, lopinavir/ritonavir demonstrates a high barrier to the development of resistance in ART-naive patients. More limited data indicate that it is effective in reducing plasma HIV-1 RNA levels in paediatric patients. Lopinavir/ritonavir has served as a well-established benchmark comparator for the noninferiority of other ritonavir-boosted PI regimens. Although overall well tolerated, lopinavir/ritonavir is associated with generally manageable adverse GI side effects and hypertriglyceridaemia and hypercholesterolaemia, which may require coadministration of lipid-lowering agents to reduce the risk of coronary heart disease. Lopinavir/ritonavir, in combination with other ART agents, is a well-established and cost-effective treatment for both ART-naive and ART-experienced patients with HIV-1 infection and, with successful management of adverse events, continues to have a role as an effective component of ART regimens for the control of HIV-1 infection.

Incidence, prevalence and diagnosis of HIV in NZ

There were typically between 150 and 180 new diagnoses of HIV infection each year between 2003 and 2010, and more diagnoses annually since 2005 than seen in the years prior to 2000, with the exception of 2011 when the number declined.[5] Over the period 2002–2011, 537 diagnoses of HIV infection were made in men who have sex with men (MSM), while 59 women and 44 men were heterosexually infected; heterosexual transmission still predominates globally.[6] The ethnicities of MSM who were diagnosed during this time closely matched the distribution of ethnicities in the NZ male population. While those infected via heterosexual transmission were mainly Europeans, the highest relative risk was seen for those of 'other' ethnicity (mainly African), and women of Māori, Pacific or Asian descent had a higher relative risk than European women. Most MSM became HIV infected in NZ, while heterosexual transmission mostly occurred overseas.

Globally, MSM have been largely refractory to preventative interventions to limit HIV transmission.[6] High-risk sexual behaviour continues in NZ and other high-income settings. One factor that may influence this is less concern due to awareness of improved disease management. Furthermore, a recent study conducted in Auckland also showed that around one in five men infected with HIV are not aware of their status.[7] The NZ *'Get it On!'* social marketing programme is designed to increase condom use in MSM during anal sex, with the main target audience being highly sexualised (at-risk) and young MSM, the latter being a group in whom declining condom use has been documented.[5] Among all HIV diagnoses in NZ (1985–2011), 2.1% and 10.1% were in individuals aged <15 years and 15–24 years, respectively.

For most individuals who are now being diagnosed with AIDS, this is also their first diagnosis of HIV infection; i.e. they have not been aware of their status and are therefore not receiving ART. Furthermore, around half of individuals diagnosed with HIV between 2005 and 2010 presented with CD4-cell counts below the recommended treatment threshold.[5] These data confirm that a large proportion of HIV-positive people are not aware of their status, and so miss the opportunity of receiving effective therapy at an early stage to prevent complications.

Disease burden

Despite the generally stable incidence of HIV infection since around the turn of the century, the burden of HIV/AIDS continues in the absence of new prevention strategies.[6] Biomedical prevention strategies are showing promise, with pre-exposure prophylaxis and early treatment with ART emerging as important for preventing spread of the virus. However, despite the relatively stable incidence of new cases of HIV infection in NZ, figures from PHARMAC show steady increases in the number of patients receiving funded ART over the last 7 years, with corresponding increases in expenditure from $8.9 million in the 2004–5 financial year to $16.8 million in 2010–11; PHARMAC currently funds 19 different antiretrovirals for HIV infection.[5] In addition, extensive resources are applied to prevention, testing, counselling, support and research programmes and initiatives by both the NZ Ministry of Health and the NZ AIDS Foundation, including the *'Get it On!'* programme and community-based rapid testing. However, the incidence has remained steady despite these interventions, and the prevalence is rising.

Pharmacokinetics of Kaletra®

While lopinavir is almost completely metabolised by cytochrome P450 (CYP)3A, ritonavir inhibits this metabolism resulting in increased lopinavir concentrations.[4] Lopinavir/ritonavir 400/100mg twice daily results in mean steady-state lopinavir plasma concentrations in patients with HIV infection that are 15- to 20-fold greater than the ritonavir concentrations. Lopinavir/ritonavir is also a potent inducer of CYP2C19 activity. Nevirapine and efavirenz lower plasma lopinavir/ritonavir concentrations in adults and children.[8]

Bioavailability of Kaletra® tablets is unaffected by concurrent food intake, while the oral solution should be taken with food to enhance bioavailability and minimise pharmacokinetic variability.[2,4] *In vitro* studies have shown that lopinavir's antiviral EC_{50} is ~10-fold lower than ritonavir's, indicating that Kaletra's® antiviral activity is the result of lopinavir. Lopinavir is 98–99% protein bound in plasma, and is eliminated mostly in the faeces (~10% in the urine) with <20% unaltered.

Registered uses, availability and profile

When initially introduced, lopinavir/ritonavir proved to be an important new therapy for patients who had failed prior therapy.[2] The wealth of information and clinical experienced associated with the use of this combination that has accumulated since then has ensured that it still has, and will continue to have, a prominent place in ART.

In NZ, Kaletra® is indicated in combination with other antiretroviral agents for the treatment of HIV1 infection in adults and children aged ≥2 years; the indication is based on HIV RNA level and CD4 cell count data from controlled clinical studies.[4] Kaletra® is available as 100mg/25mg and 200mg/50mg tablets, and is also available as an oral solution for infants weighing <7kg and patients unable to take tablets. The usual adult dosage is 800mg/200mg once daily or 400mg/100mg twice daily, but an increase to 500mg/125mg twice daily should be considered when used in combination with efavirenz, nevirapine, amprenavir or nelfinavir in treatment-experienced patients with clinically suspected reduced lopinavir susceptibly.[4,8] Paediatric dosages vary according to bodyweight or body surface area and concomitant antiretrovirals; dose increases are necessary when nevirapine or efavirenz is administered concomitantly. Care needs to be taken when prescribing lopinavir/ritonavir to patients with severe hepatic impairment as high concentrations may exacerbate this condition.[2]

Although not currently indicated in NZ, the WHO recommends, on practical grounds, that all children aged 1–2 years with HIV infection should be started on ART.[9] The available evidence suggests that a first-line regimen based on lopinavir/ritonavir is more potent than nevirapine, regardless of maternal exposure status.

New formulation – tablets versus soft gel capsules

The original soft gel capsule formulation of lopinavir/ritonavir needed to be taken with food to improve pharmacokinetics, and it required refrigerated storage.[10,11] Moreover, the excipients included oleic acid, polyethylene glycol and sorbitol, which have been linked to diarrhoea. Lopinavir/ritonavir tablets, first approved in the US in 2005, contain no oleic acid or sorbitol, do not require refrigeration, do not need to be taken with (or without) food and have less pharmacokinetic variability than the soft gel capsules. Studies have shown that not only do patients prefer the tablets over the soft gel capsules, the tablets have been associated with better adherence, quality of life measures and tolerability outcomes, including GI tolerably (stool consistency, bowel habits) and lipid levels.[10-13]

Once vs. twice daily dosing

The standard adult dosage of lopinavir/ritonavir of 400mg/100mg twice daily is currently recommended in NZ for adults with ≥3 lopinavir-associated mutations.[4] However, single daily dosing of 800mg/200mg was introduced into the NZ market in 2010, around the same time many other newer PIs and integrase inhibitors were introduced. Single daily dosing is currently indicated for adult patients with <3 lopinavir-associated mutations. In children, the once daily regimen is not recommended, as it has been shown to result in lower trough concentrations than twice daily dosing.[14] Lopinavir/ritonavir 460/115 mg/m^2 once daily has been shown to have comparable mean pharmacokinetic parameters to 800/200mg once daily in adults, but with greater variability in trough concentrations in children.[15]

Most studies have found little difference for GI tolerability of lopinavir/ritonavir between once and twice daily regimens.[1] Such studies,[16] and those that have reported high incidences of diarrhoea (e.g. Johnson et al 2006),[17] were conducted before the routine use of the tablet formulation of lopinavir/ritonavir in clinical trial settings; some trials have also allowed switching from soft gel capsules to tablets, making it difficult to interpret the tolerability findings. More recent trials using the newer tablet formulation have found that once daily dosing provides comparable virological responses to twice daily dosing with improved compliance.[18,19] In addition, once daily dosing with tablets has been found to be associated with similar or better tolerability profiles than twice daily dosing, with a more favourable lipid profile[18] and less nausea both reported.[19]

Diarrhoea

The overall incidences of GI adverse events seen in trials with lopinavir/ritonavir are generally similar to incidences seen with other PI-boosted ART regimens in both ART-naïve and -experienced patients.[1] All currently approved PIs need to be taken with ritonavir and are associated with diarrhoea.[20] While diarrhoea has been the most frequently reported adverse event associated with lopinavir/ritonavir-containing regimens,[4] it has been generally of mild-to-moderate severity and mostly reported in older studies that have used the soft gel capsule formulations.

The SWITCHMRK trials featured in this review did find a greater incidence of diarrhoea at 24 weeks with lopinavir/ritonavir tablets than with raltegravir (3% vs. 0%), but the statistical significance was not reported and the low incidence of this complication was not associated with any evidence of more discontinuations.[21] A recent meta-analysis of three trials of lopinavir/ritonavir tablets (n=1469) found that moderate-to-severe diarrhoea by treatment week 8 was reported in 11.2% of participants, and that it resolved in a median of 7.4 weeks.[20] At 48 weeks, the incidence of moderate-to-severe diarrhoea was 15.5%, but the discontinuation rate as a result was only 1.3%. The study by Molina et al featured in this review switched some participants from soft gel caps to tablets mid study, and this was found to be associated with a reduction in the incidence of diarrhoea.[13]

Zajdenverg et al (also featured) found no difference between once and twice daily dosing using the tablet formulations of lopinavir/ritonavir for the incidence

of diarrhoea (14% and 11%, respectively).[19] In comparison, the ODIN study reported respective incidences of diarrhoea of 9.9% and 15.2% for once and twice daily administration of the combination of darunavir/ritonavir;[18] darunavir has previously been shown to be associated with a low risk of diarrhoea compared with lopinavir/ritonavir at 96 weeks (4% vs. 11%), but the soft gel capsule and tablet formulations of lopinavir/ritonavir were mixed in this study.[22]

Reliable data on GI tolerability associated with the oral solution formulation of Kaletra® are scarce.

Long-term triglyceride elevation

Like other PIs, lopinavir/ritonavir is associated with elevations in total cholesterol and triglyceride levels.[4] Most recent studies have found that lipid elevations with lopinavir/ritonavir are similar to other ritonavir-boosted PIs.[1] One study found that lipid levels were reduced with lopinavir/ritonavir tablets compared with the original soft gel capsules, with the improvements confirmed to be unrelated to concomitant lipid-lowering therapy (see featured study).[12] This may explain findings of earlier trials linking lopinavir/ritonavir to greater lipid level derangements than other PIs.

Worm et al recently published a study following >33,000 patients with HIV infection followed for ~10 years showing that an increased triglyceride level was only a marginal independent predictor for increased MI risk, with a relative risk after adjusting for total and HDL-cholesterol levels and nonlipid risk factors of 1.11 (95% CI 1.01, 1.23).[23] Given the available data, patients being prescribed lopinavir/ritonavir should undergo triglyceride and cholesterol level testing before starting the regimen and at periodic intervals during treatment. The development of hyperlipidaemia on treatment with lopinavir/ritonavir can generally be managed as clinically appropriate, e.g. with lipid-lowering therapy.[1,4]

Resistance profile

The resistance profile of lopinavir/ritonavir is overall very good, with many small studies finding no evidence of phenotypic or genotypic resistance developing over long follow-up periods up to 7 years.[24-26] A high barrier to resistance is seen with lopinavir/ritonavir, with data suggesting that lopinavir/ritonavir resistance is only seen in ART-experienced patients with key primary mutation patterns within the protease gene, including mutations at L10F/I/R/V, K20M/R, L24I,M46I/L, F53L, I54L/T/V, L63P, A71I/L/T/V, V82A/F/T, I84V and L90M.[1] A recent study identified two divergent genetic pathways, one containing L76V and Q58E mutations and the other L90M and I54V mutations.[27] The lopinavir/ritonavir resistance profile in ART-naive paediatric patients appears to be consistent with that seen in adult patients.[4]

MAJOR CLINICAL TRIAL DATA FOR LOPINAVIR/RITONAVIR IN THE MANAGEMENT OF HIV-1 INFECTION

Once-daily darunavir/ritonavir vs. lopinavir/ritonavir in treatment-naive, HIV-1-infected patients: 96-week analysis[22]

Authors: Mills AM et al

Summary: ART-naïve patients with HIV-1 RNA ≥5000 copies/mL (n=689; stratified by HIV-1 RNA and CD4 cell count) received darunavir/ritonavir 800/100mg once daily or lopinavir/ritonavir 800/200 mg/day (once or twice daily dosing) and fixed-dose tenofovir/emtricitabine in the ARTEMIS phase III noninferiority trial; lopinavir/ritonavir recipients initially received soft gel capsule, but could be subsequently switched to tablets subject to availability and local approval. Viral loads of <50 copies/mL at 96 weeks (primary outcome) were seen in 79% and 71% of the darunavir/ritonavir and lopinavir/ritonavir recipients, respectively (p=0.012 for noninferiority), the respective median CD4 cell count increases were 171 and 188 cells/mL (p=0.57), and the respective rates of adverse event-related discontinuations were 4% and 9%. While the grade 2–4 treatment-related diarrhoea rate was significantly lower in the darunavir/ritonavir arm than in the lopinavir/ritonavir arm (4% vs. 11%; p<0.001), grade 2–4 treatment-related rash was infrequent in both arms and occurred at similar rates (3% vs. 1%; p=0.273). Median increases in triglyceride and total cholesterol levels were significantly smaller with darunavir/ritonavir than with lopinavir/ritonavir (0.1 vs. 0.6 mmol/L and 0.6 vs. 0.9 mmol/L, respectively; p<0.0001 for both).

Comment: ARTEMIS was the first large placebo controlled study to demonstrate superiority of one ritonavir-boosted PI over another. A subgroup analysis demonstrated that darunavir was superior to lopinavir in patients with viral loads >100,000 copies/mL (but not at lower viral loads) and those with CD4 counts <200 cells/dL (but not at higher CD4 counts). Furthermore, after excluding patients who withdrew from the study for reasons other than virological failure, darunavir remained superior, suggesting greater virological potency. The results of studies such as ARTEMIS led the DHHS guidelines committee to place darunavir ahead of ritonavir in the preferred treatment category for initial therapy.

Formulation preference, tolerability and quality of life assessment following a switch from lopinavir/ritonavir soft gel capsule to tablet in human immunodeficiency virus-infected patients[12]

Authors: Ofotokun I et al

Summary: This study enrolled patients receiving lopinavir/ritonavir-based treatment for HIV infection prior to (n=25) or 8 weeks after (n=49) switching from soft gel capsules to tablets, which contains no oleic acid or sorbitol, does not require refrigeration, has no food restriction requirements and has less pharmacokinetic variability. At 12 weeks after enrolment, significantly more participants preferred the tablet to the soft gel capsule (74% vs. 10%; p<0.0001). The Global Condition Improvement overall tolerability score was 2.46 (scale –7 to +7), with 90% of participants reporting they felt better or about the same. There were significant improvements in stool consistency (p=0.03) and Aggregate Bowel Habit-Profile scores (p=0.01), and it appeared that improved overall-tolerability was related to better GI tolerance; quality of life scores were stable. At week 12, there were significant mean reductions in: i) total cholesterol levels of 9.20 mg/dL (p=0.02); ii) triglyceride levels of 33 mg/dL (p=0.04); and iii) HDL cholesterol levels of 4.50 mg/dL (p=0.01); these were not related to lipid-lowering therapy.

Comment: The study, which was largely performed in African Americans, confirmed the benefits of Kaletra® tablets over capsules. There was improvement in stool frequency, volume and consistency, although only stool consistency reached statistical significance. The impact of GI disturbance on Kaletra® adherence has been significant, and whilst this study did not address adherence, others have demonstrated that improved tolerability does increase adherence. Other studies have failed to demonstrate a significant benefit in neither GI tolerance nor lipid prolife from switching from soft gel capsules to tablets. Some of this difference might be explained by differing study populations.

Switch to a raltegravir-based regimen versus continuation of a lopinavir-ritonavir-based regimen in stable HIV-infected patients with suppressed viraemia (SWITCHMRK 1 and 2)[21]

Authors: Eron JJ et al, for the SWITCHMRK 1 and 2 investigators

Summary: The phase III SWITCHMRK 1 and 2 studies enrolled adults with HIV infection with vRNA levels below the limit of detection for ≥3 months while receiving lopinavir/ritonavir. The participants were randomly assigned to continue lopinavir/ritonavir 400mg/100mg twice daily (evaluable n=352) or switch to raltegravir 400mg twice daily (evaluable n=350) while continuing background therapy with ≥2 NRTIs or nucleotide reverse transcriptase inhibitors. While continuing lopinavir/ritonavir was not associated with improvements in lipid levels, whereas switching to raltegravir was (1.0% vs. –12.6%, 2.6% vs. –15.0% and 6.2% vs. –42.2% for total cholesterol, HDL-cholesterol and triglyceride levels, respectively), vRNA levels <50 copies/mL were seen in a greater proportion of participants who continued lopinavir/ritonavir than those who switched to raltegravir (90.6% vs. 84.4%). Overall clinical and laboratory adverse event rates were similar between the groups and no serious drug-related adverse events or deaths were reported. Moderate-to-severe diarrhoea was seen in 3% of the lopinavir/ritonavir continuation arm, compared with no patients in the raltegravir arm. Lower than expected virological efficacy in the raltegravir arm led to trial termination at 24 weeks.

Comment: Raltegravir is the first available integrase inhibitor. Initial studies demonstrated that it had potent antiretroviral activity, was effective when given with other active agents in treatment-naive and -experienced patients, was well tolerated and had favourable effects on lipids. SWITCHMRK 1 and 2 were identically designed studies to investigate the potential to decrease PI-related adverse events through switching to raltegravir. Switching did indeed cause improvement in lipid profiles, but the study was prematurely terminated at week 24 due to a failure to demonstrate noninferiority in viral outcomes, with a significantly higher proportion of patients switching to raltegravir experiencing virological failure. Most viral isolates demonstrated mutations conferring raltegravir resistance. Subsequent analyses demonstrated that virological failure was largely seen in patients who had multiple previous therapies and/or documented resistance to other classes of drugs. The results reflected the fact that PIs like lopinavir, with a high genetic barrier to resistance, are often effective as monotherapy, whilst agents like raltegravir (and NNRTIs) require coadministration with other effective agents to avoid the rapid development of resistance and virological failure. Switching from a PI to raltegravir should be avoided when it is known or suspected that there is (archived) resistance to other components of the treatment regimen.

Similar safety and efficacy of once- and twice-daily lopinavir/ritonavir tablets in treatment-experienced HIV-1–infected subjects at 48 weeks[19]

Authors: Zajdenverg R et al

Summary: This study compared the safety and antiviral activity of lopinavir/ritonavir 800mg/200mg once daily (n=300) versus 400mg/100mg twice daily (n=299), in combination with NRTIs, in treatment-experienced patients with HIV-1 RNA >1000 copies/mL. Response rates at 48 weeks (determined by intent-to-treat time to loss of virological response) did not differ significantly between the once and twice daily groups (55.3% vs. 51.8%; p=0.413), nor did mean increases in T-cell counts or emergence of new protease resistance mutations (which was infrequent in both groups). With the exception of nausea, which was more frequent in the twice daily group, treatment-related moderate-to-severe adverse events, including diarrhoea incidence and diarrhoea-related discontinuations, were similar between the groups. Moreover, adherence was better with once daily dosing.

Comment: Adherence is clearly one of the most important determinants of successful ART. Studies have demonstrated that reducing the frequency of administration and number of pills improves adherence. Kaletra® was initially introduced as a twice daily regimen; however, subsequent studies in treatment-naïve patients (see above) have demonstrated that once daily dosing of Keletra® was as effective as twice daily dosing. In this study, a group of patients with virological failure on their current regimen were recruited to receive once or twice daily Kaletra® plus two NNRTIs. The overall low virological response rates reflect the nature of the patient population. Adherence was better in the once daily group, but this did not result in any difference in virological response. Importantly, the rate of new lopinavir mutations was similarly low in both treatment groups. This study therefore confirmed that daily Kaletra® is safe and effective.

A once-daily lopinavir/ritonavir-based regimen is noninferior to twice-daily dosing and results in similar safety and tolerability in antiretroviral-naive subjects through 48 weeks[16]

Authors: Gathe J et al

Summary: Antiretroviral-naive patients (n=664) were randomised to receive soft gel capsules or tablets of lopinavir/ritonavir, with each formulation administered once or twice daily, along with tenofovir and emtricitabine once daily; all participants randomised to soft gel capsules were switched to tablets at 8 weeks. No differences were seen between participants who received once versus twice daily dosing for: i) the proportions of participants with HIV-1 RNA <50 copies/mL at 48 weeks (77% vs. 76%; p=0.715); ii) response rates among participants with baseline HIV-1 RNA levels ≥100,000 copies/mL or when analysed according to baseline CD4+ T-cell count; iii) discontinuation rates; and iv) adverse event rates. Furthermore, no statistically significant differences were seen between the tablet and soft gel capsules for adverse event-related discontinuations, incidence of diarrhoea (any severity) or changes in lipid levels during the first 8 weeks of treatment. No new PI resistance mutations were detected out to week 48 in participants with protocol-defined virological rebound.

Comment: Pharmacokinetic studies showed that once daily administration of lopinavir/ritonavir achieved trough concentrations many times greater than the minimal inhibitory concentration for most viral isolates, suggesting that once daily dosing would be effective. This large study confirmed the results of several earlier small studies that once daily lopinavir/ritonavir had similar virological activity and side effect profile to twice daily lopinavir/ritonavir. Another aspect of this study was that during the first 8 weeks of treatment, patients were randomised to receive either lopinavir/ritonavir tablets or soft gel capsules, with all patients taking the tablets thereafter until the conclusion of the study. In contrast to some other studies (see previous) there was no significant difference in tolerability of the tablets compared with the soft gel capsules.

Once-daily atazanavir/ritonavir compared with twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naive HIV-1–infected patients: 96-week efficacy and safety results of the CASTLE study[13]

Authors: Molina J-M et al

Summary: The CASTLE noninferiority study randomised untreated patients with HIV1 infection to receive atazanavir/ritonavir 300mg/100mg once daily (n=440) or lopinavir/ritonavir 400mg/100mg twice daily as soft gel capsules (n=443), in combination with tenofovir/emtricitabine 300mg/200mg once daily. Importantly, lopinavir/ritonavir recipients were switched to lopinavir/ritonavir tablets at 48 weeks if they had experienced intolerance with the soft gel capsule formulation. Atazanavir/ritonavir was associated with a significantly greater proportion of recipients achieving HIV RNA <50 copies/mL at 96 weeks than lopinavir/ritonavir (74% vs. 68%; p<0.05). Virological failure was seen in 7% of participants in each arm at week 96. Atazanavir/ritonavir was associated with more bilirubin-associated disorders, while lopinavir/ritonavir was associated with more treatment-related GI adverse events and significantly greater changes in lipid levels at week 96 (p<0.0001). However, among the 39 participants who switched to the lopinavir/ritonavir tablet formulation, the incidence of grades 2–4 treatment-related adverse events was 8%, with no grades 2–4 treatment-related diarrhoea events after the switch and only one participant experiencing grade 1 diarrhoea.

Comment: The CASTLE study, comparing daily atazanavir/ritonavir with twice daily lopinavir/ritonavir soft gel capsules, showed similar virological efficacy after 48 weeks of treatment. This report provided results of the study's continuation to 96 weeks. Importantly, this was an open-label study, which may have affected ongoing engagement in the trial. The intention-to-treat analysis at week 96 demonstrated that the atazanavir treatment was superior to the lopinavir treatment. However, this difference was almost entirely due to the greater discontinuation rate of 22% in the lopinavir group compared with 16% in the atazanavir group. Both withdrawal of consent (18% vs. 5%) and adverse events leading to withdrawal (22% vs. 13%) were more common in the lopinavir group. The virological efficacy was similar in both groups, with 7% in both showing virological failure, and the development of resistance was very rare. Lopinavir was associated with significantly higher lipids and more GI toxicity; however, this comparison was done with lopinavir/ritonavir capsules taken twice daily. It should be noted that the more recently introduced tablet formulation taken once daily is generally associated with less side effects and better tolerability. The findings from this study confirmed an overall better safety and tolerability profile for atazanavir over lopinavir, but with similar virological activity.

Metabolic outcomes in a randomized trial of nucleoside, nonnucleoside and protease inhibitor sparing regimens for initial HIV treatment[28]

Authors: Haubrich RH et al, for the AIDS Clinical Trials Group (ACTG) A5142 Study Team

Summary: This open-label study randomised 753 patients to receive efavirenz or lopinavir/ritonavir plus two NRTIs versus the NRTI-sparing regimen of lopinavir/ritonavir plus efavirenz; zidovudine, stavudine or tenofovir with lamivudine was selected prior to randomisation. Dual-energy x-ray absorptiometry at week 96 revealed lipoatrophy in 32% of participants in the efavirenz plus two NRTIs arm, 17% of those in the lopinavir/ritonavir plus two NRTIs arm and 9% of those in the NRTI-sparing arm (p≤0.023 for all); these differences were not affected by varying the lipoatrophy definition (≥10 to ≥40% fat loss) or correction for baseline risk factors. Lipoatrophy occurred most frequently in the stavudine-containing regimens and least often in the tenofovir-containing regimens (p<0.001), with the frequency in the latter not being significantly different to that seen with the NRTI-sparing regimen. The median total cholesterol level increase at week 96 was significantly greater in the NRTI-sparing group than the other two groups (57 vs. 32–33 mg/dL), as was use of lipid-lowering agents (25% vs. 11–13%).

Comment: A surprising finding of this study was the stronger association of lipodystrophy with efavirenz in comparison with lopinavir. The strong association with stavudine, moderate association with zidovudine and weak association with tenofovir were expected. Overall, the risk of lipodystrophy in patients taking stavudine plus efavirenz was 51%, compared with a risk of 6% in those taking lopinavir plus tenofovir. Statistically, tenofovir plus efavirenz was no more likely to cause lipodystrophy than tenofovir plus lopinavir. The nucleoside-sparing regimen of efavirenz plus lopinavir showed a similarly low risk of lipodystrophy, but a very high lipogenic effect. Prior to this study, it was thought that PIs were more likely to cause lipodystrophy than efavirenz, and the findings were difficult to explain. However, they do provide reassurance over the use of lopinavir, especially been given with tenofovir as part of the nucleoside/tide backbone. The tendency of the efavirenz/lopinavir regimen to cause severe hyperlipidaemia, and no advantage over tenofovir-based regimens, limits its attractiveness for initial therapy.

Evaluation of myocardial infarction and coronary artery disease in subjects taking lopinavir/ritonavir from clinical trial and pharmacovigilance databases[29]

Authors: Da Silva B et al

Summary: These researchers found that the respective rates of MI and CAD in patients treated with lopinavir/ritonavir were 1.24 and 2.74 per 1000 participant-years for Abbott-sponsored clinical trial participants and 2.9 and 3.6 per 100,000 patient-years from pharmacovigilance reports. Most patients who experienced such events had multiple risk factors at baseline.

Comment: Multiple studies have explored the potential link of MI/coronary heart disease with antiretroviral drugs. PIs such as lopinavir/ritonavir have been strongly suspected to increase the risk of cardiac events, but the data are mixed. Two large cohort studies, D:A:D (n=33,308) and the French Hospitals Database analysis (n=74,958) found a moderate link (relative risks 1.1 and 1.33, respectively), whilst the Veterans Affairs cohort (n=36,766), the Kaiser study (n=4159) and an RCT meta-analysis (n=10,986) found no association between lopinavir and CAD. In the light of such uncertainty, this study provides some insight, and reassurance, into the cardiovascular risk associated with lopinavir/ritonavir. The analysis showed that MI and CAD in both the clinical trial and pharmacovigilance databases were relatively infrequent, and that the MI incidence was less than the age-matched incidence in the general American population (2.9 and 4.4 per 100,000 person-years in persons aged 35–74 years and 45–84 years, respectively). Almost all patients had other recognised risk factors such as smoking, hypercholesterolaemia, hypertension and diabetes, and conversely patients without these risk factors experienced a cardiovascular event very infrequently.

Concluding remarks

When first introduced in 2003, lopinavir/ritonavir proved to be a considerable advance on the first-generation PIs such as indinavir. In particular, it offered effective salvage therapy to patients with treatment failure on the available drugs at that time. Experience over subsequent years has shown that lopinavir/ritonavir remains an effective therapy with generally good tolerability and manageable toxicity. In recent years, new PIs with better tolerability and at least as good efficacy have replaced lopinavir/ritonavir as part of a preferred regimen. However, lopinavir/ritonavir remains a viable option. The development of tablets and once daily dosing makes for more convenient dosing and less GI toxicity, and recent analyses of cardiovascular risk have been reassuring. Lopinavir/ritonavir remains an effective option for treatment-naïve and -experienced patients. With many agents having similar efficacy, the decision on which therapy to offer should be individualised for each person based on knowledge of other medical conditions, including mental health issues, risk factors for cardiovascular disease, likely ability to adhere with therapy, prior therapy, known or suspected viral resistance and personal preference.

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