PRAVASTATIN DOES NOT ALTER PROTEASE INHIBITOR EXPOSURE OR VIROLOGICAL EFFICACY OVER 24 WEEKS THERAPY.

Moyle GJ, Buss NE*, Gazzard BG. Chelsea and Westminster Hospital, London UK and *Roche, Basel, Switzerland.
Correspondence to Dr Moyle. 369 Fulham Rd London SW10 9NH UK
Email: gm@moyleg.demon.co.uk

ABSTRACT:

Introduction: Amongst cholesterol lowering statins pravastatin is thought to have the least impact on cytochromes P450. The efficacy of pravastatin plus dietary advice in persons receiving protease inhibitors (PIs) is similar to efficacy observed in persons with endogenous hyperlipidaemia, reducing LDL cholesterol by approximately 20%.
Methods: Patients on PI therapy with viral load <500cps/ml were randomised to either dietary advice alone or dietary advice plus pravastatin 40mg qd. Samples for PI levels were taken pre-dose (trough) and one hour post observed dosing, before the randomisation and at weeks 12 and 24 of randomised therapy.
Results: 31 male patients were randomised, 15 to pravastatin therapy and 16 to dietary advice alone. All patients remained <500cps/ml throughout 24 weeks study. According to an analysis of variance model (ANOVA) levels of log transformed ritonavir (n=8), indinavir (n=5) and saquinavir (n=6) at both pre-dose and post-dose did not change significantly (p>0.05 for all comparisons) between baseline and week 24 in persons receiving praovastatin. Paired median pre-dose levels at baseline and week 24 were: ritonavir 1176 and 1439, indinavir 116 and 149 and saquinavir 247 and 386ng/ml. Similarly, no changes in PI exposure were observed in the dietary advice alone arm.
Conclusions: Consistent with studies in healthy volunteers, no impact of pravastatin on PI trough and post-dose exposures were seen in the study. Efficacy and lack of interactions with pravastatin suggest this agent to be first line choice in hypercholesterolaemia in persons receiving PI-based HAART.

INTRODUCTION:

Dyslipidemia in persons receiving current antiretroviral therapy including regimens containing current HIV protease inhibitors (PIs) is common and may increase over time on therapy. The elevation in cholesterol is principally in the LDL and VLDL fractions and in healthy volunteers has been suggested to be related to increased hepatic production of VLDL[1]. HMG-CoA reductase inhibitors ('statins') are the current standard of care for persons with primary hypercholesteroaemia. HMG-CoA-reductase in the liver is the key rate controlling enzyme in the de novo synthesis of cholesterol, the mechanism responsible for production of >50%of total body cholesterol. Inhibition of HMG-CoA reductase activatesresults in an increased synthesis of hepatic LDL-receptors leading to increased clearance of circulating LDL[2]. Pravastatin may represent the best statin to use with PIs as, unlike other statins, it is lessnot substantially metabolised by cytochromes p450 (CYP), and specifically, not to any clinically meaningful extent by CYP3A4 the enzyme responsible for the bulk of PI metabolism. Additionallyto any clinically meaningful extent, , pravastatin has the lowest binding to plasma proteins of the statin agents[3]. Significant drug interactions with protease inhibitors have not been observed although a trend to lower pravastatin exposures is seen when combined with ritonavir plus saquinavir[4]. The efficacy of pravastatin plus dietary advice in persons receiving protease inhibitors (PIs) is similar to efficacy observed in persons with endogenous hyperlipidaemia, reducing total cholesterol by 17.3%[5]. Additional interest in statins has recently been generated following reports from an *in vitro* studie that these agents may diminish the ability of HIV to be released from infected cellshave antiretroviral activity[6].

METHODS:

Patients on single or dual PI therapy, with 2 nucleoside analogs, for greater than 12 weeks and with viral load <500cps/ml and cholesterol >6.5mmol/l (240mg/dl) were randomised to either dietary advice alone or dietary advice plus pravastatin 40mg qd[5]. Samples for PI levels were taken pre-dose (trough) and one hour post observed dosing, before randomisation and at weeks 12 and 24 of therapy. Samples were frozen and batch processed at the end of the study by Professor David Back, University of Liverpool, UK, using established high performance liquid chromatography methodology.
Statistical analysis of the protease inhibitor plasma concentrations wereas performed using an analysis of variance model (ANOVA) of the log transformed values. The analysis was performed separately for each of the two groups (pravastatin or dietary advice alone) and for each treatment (saquinavir, indinavir, ritonavir and nelfinavir).

Table 1. Log_{10} Concentration of PI (ng/ml or µg/L) by randomisation group (Pravastatin (P) or dietary advice (DA) over time.

Drug and Randomisation (N) pre and 1 hour post dose		Baseline (mean) and 95%CI)	Week 12	Week 24
Indinavir +P (n=5)	Pre Post	4.94 (3.55-6.34) 8.52 (8.2-8.85)	5.62 (4.25-6.98) 8.15 (7.09-9.02)	5.04 (4.33-5.75) 7.21 (3.87-6.08)
Indinavir +DA (n=4)	Pre Post	5.31 (4.55-6.07) 8.67 (8.04-9.3)	5.14 (4.45-5.84) 8.74 (8.34-9.13)	5.27 (4.56-5.98) 8.81 (8.08-9.53)
Ritonavirr +P (n=8)	Pre Post	6.89 (6.26-7.52) 7.99 (7.35-8.63)	6.64 (6.29-6.99) 7.62 (6.74-8.51)	6.94 (6.38-7.49) 7.74 (6.99-8.49)
Ritonavir +DA (n=4)	Pre Post	6.69 (5.23-8.15) 8.36 (7.27-9.45)	6.67 (5.35-7.99) 7.89 (6.69-9.08)	6.04 (3.98-8.11) 6.58 (5.29-7.87)
Saquinavir +P (n=6)	Pre Post	5.5 (5.04-5.97) 6.11 (5.47-6.75)	4.77 (3.96-5.57) 6.27 (5.54-7.0)	5.64 (4.6-6.68) 6.66 (6.21-7.11)
Saquinavir +DA (n=3)	Pre Post	4.79 (3.74-5.84) 5.38 (3.66-7.11)	4.51 (2.63-6.38) 5.27 (4.05-6.49)	2.98 (-021-6.18) 5.28 (5.16-5.41)
Nelfinavir +DA (n=4)	Pre Post	7.26 (6.28-8.23) 7.37 (6.38-8.37)	7.63 (6.87-8.39) 7.55 (6.86-8.24)	4.56 (0.91-8.21) 7.24 (5.93-8.54)*

*n=3

RESULTS:

31 male patients were randomised, 15 to pravastatin (PS) therapy and 16 to dietary advice (DA) alone. One patient in the DA arm withdrew before week 12. A further 4 patients (3 on DA, 1 on PS) withdrew between weeks 12 and 24, all for personal reasons. No severe or serious adverse events or changes in laboratory parameters were reported. Baseline demographics were well matched with no significant differences in age, CD4, weight, BMI, and lipids[5]. All patients remained <500cps/ml throughout 24 weeks study. Details of drug exposures at baseline, week 12 and 24 are shown by randomisation and by PI in table 1. Data on the single patient in the pravastatin arm who was receiving nelfinavir are not included.
Paired median pre-dose levels at baseline and week 24 were: ritonavir 1176 and 1439, indinavir 116 and 149 and saquinavir 247 and 386ng/ml. According to an analysis of variance model (ANOVA) levels of log transformed ritonavir (n=8), indinavir (n=5) and saquinavir (n=6) at both pre-dose and post-dose exposures did not change significantly (p>0.05 for all comparisons) between baseline and week 24 in persons receiving pravastatin. Similarly, no significant changes in PI exposure were observed in the dietary advice alone arm.

CONCLUSIONS:

Consistent with studies in healthy volunteers[4], no impact of pravastatin on PI trough and post-dose exposures were seen in the study. Additionally, all patients remained with viral load <500 copies/ml throughout the study. Significant interactions with simvastatin have been reported with levels of the drug statin rising up to 27-fold in the presence of ritonavir 400mg plus saquinavir 400mg bid at steady state. An elevation of atorvastatic acid (the active form of atorvastatin) levels of 76% with this combination suggests it should be used with caution[4]. Interactions of statins with non-nucleoside reverse transcriptase inhibitors have not been described. As nevirapine and efavirenz are predominately inducers of CYP3A it is likely that they will not effect pravastatin greatly but may reduce exposure of statins metabolised by CYP3A to a greater extent, such as atorvastatin and simvastatin.
Declines in total and LDL cholesterol with pravastatin reported in this study were consistent with data reported in enogenousendogenous hyperlipidemia[5].
The efficacy and lack of significant drug interactions with pravastatin suggest this agent to be first line intervention choice in hypercholesterolaemia in persons receiving PI-based HAART.

ACKNOWLEDGEMENTS:

Thanks to Brian Reynolds, Michelle Lloyd and Christine Baldwin for assistance I study conduct.

RESULTS:

1. Purnell JQ, Zambon A, Knopp RH, et al. Effect of ritonavir on lipids and post-heparin lipase activities in normal subjects. AIDS 2000;14:51-57.
2. Grundy SM Cholesterol metabolism in man. West J Med 1978;128;13-25
3. Pentikainen PJ, Saraheimo M, Schwartz JI, et al. Comparative pharmacokinetics of lovastatin, simvistatin and pravastatin in humans. J Clin Pharmacol 1992;32:136-140.
4. Fichtenbaum C, Blaschke T, Rosenkranz S, et al. Pharmacokinetic interactions between protease inhibitors and selected HMG-CoA reductase inhibitors. XIII International AIDS conference, Durban, July 9-14, 2000: abstract WeOrB544..
5. Moyle G, Lloyd M, Reynolds B, Baldwin C, Mandalia S, Gazzard BG. An open label, randomized trial of dietary advice with or without pravastatin for the management of protease inhibitor associated hypercholesterolaemia. AIDS 2001;15:1503-1508.
6. Ono A, Freed EO. Plasma membrane rafts play a critical role in HIV-1 assembly and release. Proc Nat Acad Sci USA 2001; 98:13925-13930.