

# Lipid Profiles of Patients Enrolled in the MaxCmin2 Trial: A Randomized, Open-Label, Multicenter Comparative Trial Evaluating the Safety and Efficacy of lopinavir/ritonavir (LPV/r; 400/100 mg bid) versus saquinavir/ritonavir (SAQ/r; 1000/100 mg bid)

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## BACKGROUND:

Ritonavir-boosted protease inhibitors are increasingly being used as part of HAART in the management of ARV naïve and experienced HIV infected patients. Few randomised comparative trials are available that evaluate the relative efficacy and tolerability of different ritonavir-boosted PI strategies. The MaxCmin2 trial was a 48 week randomised open-label multi-centre study in which patients were randomised to receive lopinavir/ritonavir (LPV/r; 400mg/100mg bid) or saquinavir/ritonavir (SAQ/r; 1000/100 mg bid) (Figure 1). In the primary intention to treat analysis including patients exposed to the study drugs (ITT/e population) the risk of protocol defined virologic failure was significantly greater in the SAQ/r arm (33%) than the LPV/r arm (18%) (log rank test: p=0.002). However, there were no differences in response rates in the on treatment analysis (log rank test: p=0.27) and a similar proportion of patients had virologic suppression to < 50 copies/ml at 48 weeks in the ITT/e analysis (65% vs. 57%, p=0.12).

In MaxCmin2 no differences were seen between the study arms in the number of grade 3/4 adverse events or in time to development of a grade 3/4 adverse events.

## OBJECTIVES

A pre-planned intention-to-treat (ITT) analysis of lipid changes in patients who were exposed to (initiated) the assigned treatment (ITT/e population) in the MaxCmin2 trial.

## METHODS

Fasting total cholesterol (TC), LDL cholesterol (LDL) and triglycerides (TG) were measured at baseline and weeks 4 and 48. Percentage changes from baseline were compared using Kruskal-Wallis non-parametric tests. Logistic regression was used to identify predictors of abnormal values at certain time points throughout the study with a significance level of 5%. We considered the following ranges to be normal for the parameters under investigation: TC: 3.4 - 6.2 mmol/l, LDL: 1.7 - 3.2 mmol/l and TG: 0.5 - 2.3 mmol/l.

## RESULTS

A total of 324 patients initiated their assigned treatment including 163 randomised to LPV/r and 161 randomized to SAQ/r. No differences were seen between study arms in baseline characteristics (data not shown).

The proportion of patients with abnormal TC values at baseline was low and without difference between the study arms, 11% in the LPV/r arm and 13% in the SAQ/r arm, respectively (Figure 2). The proportion of patients with abnormal LDL and TG values at baseline high, 31% and 25% in the LPV/r arm and 28% and 35% in the SAQ/r arm, respectively (Figure 2).

The proportion of patients with abnormal TC values increased at Week 4 in both arms and remained stable through Week 48 (20% in both study arms; p=n.s.). The proportion of patients with abnormal LDL values remained stable at weeks 4 (35%) and 48 (31%) in the LPV/r arm but was increased at Week 4 (48%) and 48 (49%) in the SAQ/r arm. Conversely, the proportion of patients with abnormal TG values was increased at Week 4 (48%) and 48 (46%) in the LPV/r arm but remained stable at weeks 4 (32%) and 48 (35%) in the SAQ/r arm. Furthermore, significantly higher increases in median percentage change from baseline in LDL cholesterol was seen in the SAQ/r arm (p-value Week 4/48: <0.0001/0.06). Conversely, higher increases in median percentage change from baseline in TG was seen in the LPV/r arm (p-value Week 4/48: 0.0005/0.0004) (Figure 2 & 3). LDL cholesterol cannot be reliably assessed in many patients if the TG level is > 4.5 mmol/l. The proportion of patients with missing LDL values because of increased TG > 4.5 mmol/l at baseline, week 4 and 48 was 7/11, 9/16 and 18/26 in the LPV/r arm and 4/13, 9/15 and 7/12 in the SAQ/r arm, respectively.

Use of a lipid lowering agent (LLA) could influence the above parameters, however only 5 patients in each study arm used LLA at some point during follow-up (Table 2).

Table 2: Patients who received a lipid lowering agent at baseline and/or during follow-up

	LPV/r (No., %)			SAQ/r (No., %)		
	Statin	Fibrate	Fish oil	Statin	Fibrate	Fish oil
Baseline	1 (1)	2 (1)	0 (0)	1 (1)	0 (0)	1 (1)
Follow-up	3 (2)	1 (1)	1 (1)	1 (1)	4 (2)	0 (0)

Regression models were constructed to assess the influence of baseline characteristics, the use of LLA and clinical lipodystrophy on lipid elevations. Independent predictors of having an elevated triglyceride level at Week 48 were treatment, use of d4t at baseline, BMI, and race (Table 1).

## CONCLUSIONS

- Lipid abnormalities were common in patients enrolled in the Maxcmin2 trial but they were typically mild and resulted in the use of LLA in a minority
- Patients randomised to LPV/r had a 29% median increase in TG over the study, whereas median TG did not increase in the patients randomized to SAQ/r
- There were insignificant % increases in both study arms in LDL-cholesterol but as many patients could not have LDL measured because of increased TG (more in LPV/r arm) the significance of this is unclear

Figure 1

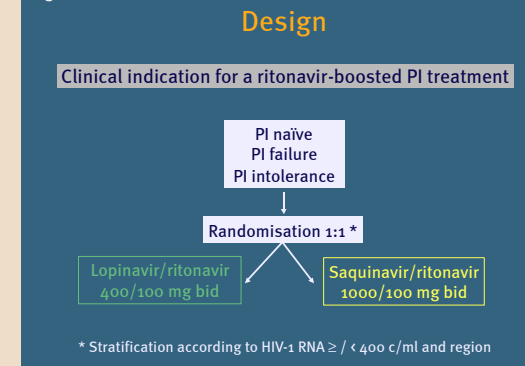


Figure 2

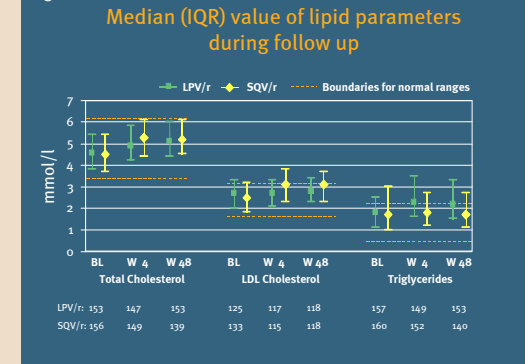


Figure 3

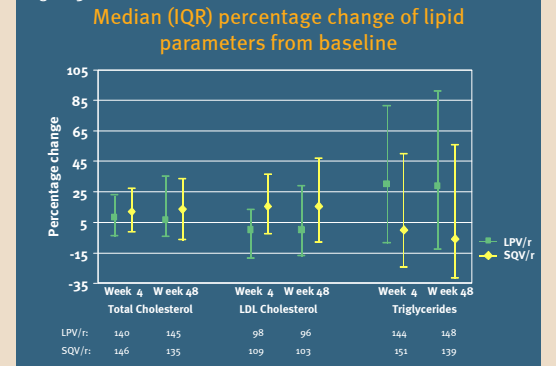


Table 1

Risk of having a high triglyceride level at Week 48 (logistic regression model)

Variable	Single variable analysis		Multi variable analysis	
	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
Treatment (LPV/r v SQV/r)	1.6 (1.0-2.6)	0.05	1.7 (1.0-2.8)	0.04
Use of d4t at baseline (Yes/No)	1.7 (1.0-2.8)	0.06	1.8 (1.0-3.2)	0.04
BMI category (kg/m <sup>2</sup> )		0.008		0.0006
20 - 24.9	1.0 (1)		1.0 (1)	
25 - 29.9	2.6 (1.1-6.1)		3.3 (1.4-7.8)	
30 - 34.9	5.0 (2.0-12.7)		7.6 (2.9-20.0)	
35 - 39.9	1.9 (0.5-8.1)		5.2 (1.1-24.7)	
≥ 40	2.6 (0.4-16.2)		4.2 (0.5-36.7)	
Race		0.0008		0.0001
White	1.0 (1)		1.0 (1)	
Black	0.3 (0.1-0.6)		0.2 (0.1-0.4)	
Other	1.2 (0.4-3.3)		1.3 (0.4-4.5)	

Other factors that were significant in the single variable analysis were the mode of transmission (OR: 1.4 for HIV2, p=0.03), gender (OR: 0.4 for females, p=0.01), the baseline CD4 cell count (OR: 1.1 per 100 cells/ml higher, p=0.09) and the presence of lipodystrophy at baseline (OR: 4.5 for subjects with lipodystrophy, p=0.07).

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