HAART simplification with lopinavir/ritonavir monotherapy in HIV/HCV co-infected patients starting anti-HCV treatment: a randomised pilot study (KaMon study)

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SUMMARY

The aim of this randomised, prospective, open-label, multicentre pilot clinical trial was to compare the 48-week toxicity profile of lopinavir/ritonavir (LPV/r) monotherapy with LPV/r–based HAART (KaMon = Kaletra monotherapy) in HIV/HCV patients undergoing HCV treatment. The study involved 30 HIV/HCV co-infected patients naïve to anti-HCV therapy. One patient in each arm (6.7%) discontinued anti-HCV therapy because of adverse events. There were no significant between-group differences in terms of the proportion of patients experiencing AEs (p=0.999) or the number of grade 3-4 AEs (p=0.146). No HIV failure was observed.
The safety profile of LPV/r monotherapy was similar to that of LPV/r–based HAART, thus encouraging HAART simplification in patients receiving anti-HCV treatment.

KEY WORDS: HAART-simplification strategy, Anti-HCV drugs, LPV/r monotherapy, Tolerability of HIV/HCV treatments.

Received March 20, 2012 *Accepted* August 05, 2012

The fact that one-third of HIV-positive patients are co-infected with HCV gives rise to a significant burden in terms of morbidity and mortality (Rockstroh *et al.*, 2004). The concomitant use of drug regimens to control both infections may increase the incidence and severity of adverse events (AEs), which have been associated with a higher 6-year mortality rate (Keiser *et al.*, 2007). For this reason new therapeutic strategies aimed at reducing the incidence of drug-related AEs are encouraged provided that their efficacy and safety profiles are comparable with those of HAART.

Monotherapy with protease inhibitors (PIs) such as lopinavir, atazanavir and darunavir has been proposed as a mean of simplifying long-term HAART regimens and reducing AEs. The pharmacokinetics, dosing and tolerability of ritonavir-boosted PIs makes them effective and safe (Perez-Valero *et al.*, 2011), and randomised controlled trials (RCTs) comparing ritonavir-boosted lopinavir (LPV/r) monotherapy with HAART have shown that they can maintain viral suppression for up to four years (Arribas *et al.*, 2009; Pulido *et al.*, 2008; Pulido *et al.*, 2008b; Nunes *et al.*, 2009; Marcotullio *et al.*, 2012). Although a systematic meta-analysis of data from six RCTs found that virological failure was more frequent with LPV/r monotherapy than HAART (Bierman

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et al., 2009), the fact that HIV rebounds were completely suppressed by the reintroduction of HAART without the emergence of drug resistance confirms the feasibility and safety of this PI-based regimen (Arribas *et al.*, 2009; Pulido *et al.*, 2008b).

The European AIDS guidelines currently permit PI-based monotherapy with LPV/r twice daily or darunavir/ritonavir (DRV/r) once daily in patients who are intolerant to nucleoside reverse-transcriptase inhibitors (NRTIs) or as a means of simplifying treatment in subjects with a viral load of <50 copies/mL in the previous months and without a history of failure on previous PI-based therapy (Antinori *et al.*, 2011; EACS, 2011; Morsica *et al.*, 2011).

The clinical role of a simplification strategy is still debated, and its potential usefulness in HIV/HCV patients simultaneously receiving HAART and anti-HCV drugs has not yet been investigated. The aim of this multicentre, randomised, prospective, open-label, controlled pilot clinical trial was to compare the 48-week toxicity profile of LPV/r monotherapy with that of LPV/r-based HAART in HIV/HCV patients undergoing anti-HCV therapy (KaMon = Kaletra monotherapy study).

Thirty-six patients were screened. The inclusion criteria were an age of >18 years, a confirmed diagnosis of HIV/HCV co-infection, the absence of previous anti-HCV treatment, a Child-Pugh score of A (for patients with liver cirrhosis), a CD4+ cell count of ≥350 cells/mm^3, stable HAART and HIV RNA levels of <50 copies/mL for at least six months, and the absence of previous PI mutations or previous virological failure on PI-based treatment. Thirty patients (83%) met the inclusion criteria, and were randomised to receive LPV/r monotherapy (arm A: LPV/r 400/100 mg b.i.d.) or HAART (arm B: LPV/r and tenofovir/emtricitabine) plus anti-HCV therapy (pegylated interferon-alpha 2a [Peg-IFN] plus ribavirin 0.8-1.2 g/day, based on body weight). During follow-up, the patients could receive concomitant supportive medications such as granulocyte colony-stimulating factor (G-CSF) and erythropoietin.

The study was conducted in accordance with the Good Clinical Practice guidelines and the ethical principles stated in the Declaration of Helsinki. The enrolled patients gave their written informed consent, and the study was approved by the Ethics Committees of all of the participating institutes (ClinicalTrials.gov registration No. NCT00437684).

The patients were followed up for 72 weeks (48 weeks of concomitant HIV/HCV therapy, followed by 24 weeks of HIV treatment alone), and evaluated after 2, 4, 8, 12, 24, 48, 60 and 72 weeks. The primary endpoint was the proportion of patients who reduced or stopped anti-HCV therapy after up to 48 weeks because of at least one AE, including hematological AEs (hemoglobin <8g/dL, absolute neutrophil count <750 cells/mm^3, platelets <20000/mm^3), severe neuropsychiatric AEs (depression, irritability, insomnia), weight loss (>15% of baseline value), mitochondrial toxicity (grade 3-4 hyperlactatemia, grade 3-4 pancreatic enzyme levels), hepatic impairment (ascites, bleeding esophageal varices, encephalopathy, spontaneous bacterial peritonitis, hepatocellular carcinoma), and other less common AEs such as thyroid dysfunction. The secondary endpoints (evaluated after 12, 24, 48 and 72 weeks) were HIV and HCV virological responses (HIV RNA <50 copies/mL or HCV RNA <12 IU/mL), significant changes in biochemical parameters, the proportion of patients experiencing AEs, and plasma LPV concentrations (C_{trough} at baseline and after 4, 12, 48 and 72 weeks).

The primary statistical analysis (safety and immunovirological parameters) was made using the intention-to-treat (ITT) principle and the last observation carried forward (LOCF) method, whereas the analysis of virological efficacy was made using the on-treatment (OT) principle. The results are given as median values and interquartile ranges (IQR) or frequencies (%), as appropriate. The patients' baseline and follow-up characteristics were compared between the two arms using the Wilcoxon rank-sum test or the chi-square/Fisher's exact test. Bonferroni corrections were made when dealing with multiple comparisons. The proportion of subjects who reduced or stopped HCV treatment in the two groups was compared using the chi-square test, and the 95% confidence interval (CI) of the difference was also estimated. A two-sided alpha level of 0.05 was considered statistically significant. The analyses were made using SAS statistical software version 9.2 (SAS Institute, NC, USA).

The thirty patients were equally randomised to the treatment arms. Age (arm A 44 [42-46] *vs* arm B 48 [45-53] years; p=0.055), gender (males arm A 10 [67%] *vs* arm B 11 [73%]; p=0.690), risk factors (injective drug users arm A 9 [60%] *vs* arm B 10 [67%]; p=0.763), CDC stage (stage C: arm A 5 [33%] *vs* arm B 3 [20%]; p=0.902), nadir CD4 count (arm A 71 [28-247] *vs* arm B 181 [90-266] cells/µl; p=0.263), duration of HIV infection (arm A 19 [17-20] *vs* arm B 21 [14-24] years; p=0.759) and HCV genotype (genotype 1-4/2-3: arm A 6/9 *vs* arm B 9/6 patients; p=0.474) were similar between the two groups. Their main immunovirological and biochemical characteristics are shown in Tables 1 and 2.

Eleven patients (36.6%) discontinued the study, and 19 (63.4%) completed the follow-up. One patient in each arm (6.7%; 95%CI of the difference between proportions from -0.108 to +0.108) stopped anti-HCV therapy because of AEs: the patient in arm A because of anemia, fatigue, weight loss and mucositis after 24 weeks, and the patient in arm B because of anemia and neutropenia after 12 weeks. Seven patients (23.3%) discontinued treatment due to HCV virological failure: four patients in arm A (27%: one after 12 weeks, and three 24 weeks), three patients in arm B (20%) after 24 weeks. Finally, one patient in each arm (6.7%) was lost to follow-up.

Although there were no significantly different changes in biochemical parameters between arms A and B, some values tended to improve over time (AST, ALT, gamma-GT levels), and others (total cholesterol and triglycerides) tended to worsen, mainly in arm A (Table 2). Plasma (C_{trough}) LPV concentrations remained stable in both arms throughout the study (Table 2).

Twenty-seven patients (90%) experienced at least one AE: 13 in arm A (87%) and 14 in arm B (93%). There was a total of 114 AEs (a median of 4 [2-5] per patient): 71 (4.5 [3-5]) in arm A, and 43 (3 [2-4]) in arm B. There were no significant between-group differences in the proportion of patients experiencing at least one AE (p=0.999) or in the number of AEs (p=0.146). Nine patients experienced 14 grade 3-4 AEs: five in arm A (four cases of anemia and two of neutropenia), and four in arm B (three cases of neu-

TABLE 1 - *Haematological, immunovirological and pharmacokinetic characteristics of the patients in the two study arms*

Characteristics	*Baseline*			*48 weeks*			*72 weeks*		
	Arm A	*Arm B*	*P value*	*Arm A*	*Arm B*	*P value*	*Arm A*	*Arm B*	*P value*
Haemoglobin, g/dL	14 (13-14.5)	15.3 (14-16)	0.017	11 (11-12.3)	12 (11.6-13)	0.059	13 (12.4-14)	14 (12.4-15)	0.085
WBC, x10^3 cells/µL	6 (4.8-7)	5.85 (5.1-7.3)	0.793	2.7 (1.8-3.7)	3 (1.8-5)	0.339	5.5 (3.7-7)	5 (3.7-6.5)	0.958
ANC, x10^3 cells/µL	3 (2.5-3.5)	2.8 (2.4-4.5)	0.615	1.4 (1.0-1.7)	1.5 (0.9-2.8)	0.395	2.8 (1.9-4.2)	2.5 (1.9-5.01)	0.676
CD4 count, cells/µL	585 (399-806)	524 (433-749)	0.619	267 (183-474)	321 (272-432)	0.384	556 (340-633)	456 (417-553)	0.305
HCV RNA, Log IU/mL	6.18 (5.71- 6.46)	5.37 (4.24-6.32)	0.159	1.04 (1.04-4.52)	1.04 (1.04-2.69)	0.539	1.04 (1.04-4.86)	1.04 (1.04-4.29)	0.984
HIV RNA, copies/mL	49 (49-49)	49 (49-49)	0.351	49 (49-49)	49 (49-49)	0.351	49 (49-49)	49 (49-49)	0.407
Lopinavir C_{trough}, ng/mL	5529 (4506-6839)	7114 (5323-8449)	0.431	6330 (3919-6900)	6805 (5400-10000)	0.438	5573 (3268-6796)	5688 (4267-8177)	0.447

WBC = White Blood Cells; ANC = Absolute Neutrophil Count. Median (Q1-Q3) value or frequency (%).

tropenia, two of anemia, and one case each of thrombocytopenia, rash and fatigue). Most of the grade 1-2 AEs affected bone marrow function (anemia, neutropenia), the skin and mucosa (rash, mucositis), and mental status (irritability).

An early virological response (EVR) to anti-HCV therapy was observed in 15/30 patients (50%: 8/15 in arm A, and 7/15 in arm B), 87% of whom were infected by HCV genotype 2-3 (arm A: 8/9; arm B: 5/6). A sustained virological response (SVR) was achieved by 15/19 patients (arm A: 7/9; arm B: 8/10), 12 (80%) of whom were infected by HCV genotypes 2-3.

There was no HIV virological failure; only one patient (arm B) experienced a virological blip after 12 weeks that resolved without modifying the antiretroviral therapy.

TABLE 2 - *Biochemical parameters of the patients in the two study arms.*

	Baseline			*48 weeks*			*72 weeks*		
	Arm A	*Arm B*	*P value*	*Arm A*	*Arm B*	*P value*	*Arm A*	*Arm B*	*P value*
ALT, U/L	66 (52-137)	85 (39-113)	0.868 (18-40)	28	27 (24-52)	0.281	22 (20-29)	29 (16-63)	0.281
AST, U/L	42 (35-99)	42 (33-56)	0.983	25 (22-33)	26 (23-36)	0.755	22 (20-23.5)	22 (16-30)	0.860
Lactic acid, mmol/L	1. (0.84-1.03)	1.3 (0.84-1.6)	0.111	1.1 (0.80-1.5)	0.93 (0.8-1.37)	0.442	0.87 (0.6-1.5)	0.93 (0.9-1.45)	0.476
Total bilirubin, mg/dL	0.87 (0.7-1.03)	0.86 (0.7-1.11)	0.760	0.51 (0.4-0.8)	0.59 (0.3-0.8)	0.967	0.75 (0.45-0.8)	0.6 (0.32-0.76)	0.475
Gamma-GT, U/L	104 (46-152)	91 (46-174)	0.787	39 (29-121)	37 (28-49)	0.372	52 (31.5-66)	27 (24-56)	0.099
Amylase, U/L	33 (30-40)	38 (34-62)	0.385	29 (27-55)	45 (24-61)	0.469	56 (29-76)	38 (24-61)	0.620
Albumin, g/L	42 (39-45.4)	43.1 (41.3-46)	0.489	41 (36.2-44.7)	42.2 (41-45.4)	0.158	43 (41.3-43.2)	44 (41-46)	0.258
Fasting insulin, mIU/L	12 (6-17)	16.0 (9.2-19)	0.209	12.4 (7-17)	18.8 (10.6-26)	0.152	13.9 (8.6-16.5)	18.8 (10.6-26)	0.131
Fasting glucose, mg/dL	80 (76-85)	88 (84-95)	0.917	77 (72-83)	84 (77-88)	0.051	87 (82-87)	89 (84-93)	0.069
Total Cholesterol, g/dL	162 (153-196)	176 (160-205)	0.290	174 (153-200)	175 (153-192)	0.820	199 (173-251)	190 (162-205)	0.231
HDL-cholesterol, mg/dL	44 (29-49)	44 (40-50)	0.279	35.5 (33-46)	39 (33-48)	0.570	43 (33-43)	39 (33-53)	0.717
LDL-cholesterol, mg/dL	84 (69-101)	98 (82-120)	0.167	79 (71-111)	88 (68-119)	0.371	108 (72-156)	109 (80-118)	0.856
Triglycerides, mg/dL	129 (97-149)	138 (105-199)	0.431	189 (128-311)	157 (128-230)	0.694	249 (135-258)	156 (119-224)	0.122

ALT = Alanine transaminase; AST = Alanine Aminotransferase; HDL = High-Density Lipoprotein; LDL = Low-Density Lipoprotein. Median value and interquartile range (Q1-Q3).

To the best of our knowledge, the KaMon study is the first to evaluate the safety and efficacy of HAART simplification with PI monotherapy in subjects receiving anti-HCV treatment with Peg-IFN and ribavirin. The proportion of patients who withdrew from the study because of toxicity was small and similar in both arms, thus supporting the hypothesis that LPV/r monotherapy during anti-HCV treatment may be as safe and effective as LPV/r-based HAART.

HIV viral loads were almost suppressed in all of the subjects throughout the study, as has also been observed in other LPV/r monotherapy trials (Arribas *et al.*, 2009; Pulido *et al.*, 2008; Nunes *et al.*, 2009). One patient in arm B experienced a transient blip that resolved spontaneously, whereas all of the patients receiving PI monotherapy maintained a plasma HIV RNA concentrations that were below the detection limit, thus suggesting optimal virological control.

The main limitation of the KaMon study is its small sample size and consequently the low power to detect differences between the study arms. Nonetheless, the results are encouraging as PI monotherapy does not seem to be inferior to PI-based HAART in controlling HIV replication during anti-HCV therapy. If treatment with Peg-IFN plus ribavirin (alone or in combination with direct antiviral agents) is started, the antiretroviral regimen may need to be modified in order to reduce potential drug-drug interactions, drug toxicities, and/or the number of pills. In this scenario, PI monotherapy can ensure adequate control of HIV without affecting the response to anti-HCV therapy while concomitantly limiting drug toxicity and the daily pill burden.

ACKNOWLEDGEMENTS

This study was supported by a grant from Abbott. The funding source played no role in the study design, data collection, data analysis and interpretation, the preparation of the manuscript, or the decision to submit the manuscript for publication. We would like to thank the patients who participated to the study.

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