Brighton and Sussex Clinical Trials Unit

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Results of Hepmarc: a 96-week feasibility trial of add-on maraviroc in people with well-controlled HIV and NAFLD

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INTRODUCTION

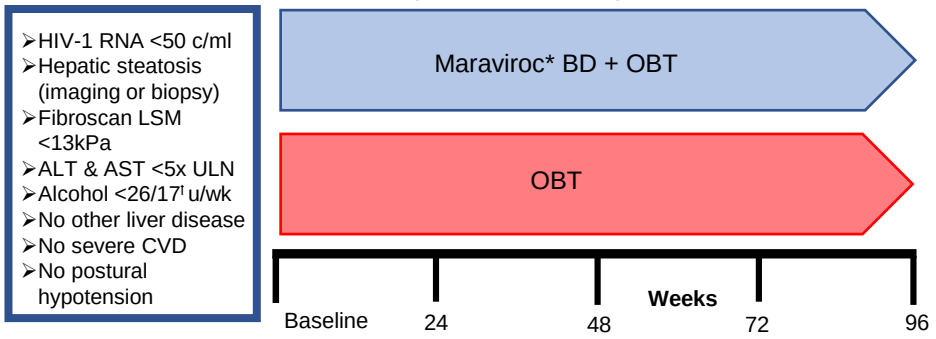
Non-alcoholic fatty liver disease (NAFLD) affects ~35% of people with HIV and may progress to steatohepatitis, cirrhosis and hepatocellular carcinoma. Treatments largely involve lifestyle changes, which are difficult to achieve, and pharmacological therapies are urgently needed. Chemokine (C-C motif) ligand 5 (CCL5), the ligand for C-C chemokine receptor type 5 (CCR5), plays a key role in hepatic inflammation and antagonism of the CCR5-CCL5 pathway could therefore reduce liver inflammation and fibrosis. The CCR5 receptor antagonist, Maraviroc (MVC), is licensed for HIV-1 treatment as part of combination antiretroviral therapy (cART), where the infecting strain is CCR5 tropic. MVC inhibits HIV-1 gp120 binding to the CCR5 co-receptor, preventing virus entry into cells. Its antagonism of the CCL5-CCR5 pathway raises the possibility of additional anti-inflammatory effects.

Although maraviroc represents a potential treatment for HIV-NAFLD, dosing is usually twice daily, unlike currently recommended antiretrovirals. We therefore conducted a randomised controlled trial (RCT) to evaluate the safety, acceptability and feasibility of maraviroc add-on therapy to cART in HIV-NAFLD.

METHODS

We carried out a multicentre, open-label, feasibility, randomised controlled trial in adults with well-controlled HIV-1 on cART and NAFLD (Figure 1). Randomisation was in a 1:1 ratio stratified by (1) history of ≥ 6 months' exposure to a protease inhibitor (2) BMI ≥ 25 (3) type 2 diabetes mellitus status (4) current exposure to lipid-lowering agents.

Figure 1. Trial design



*dosed as per Summary of Product Characteristics, [†] in men / women respectively, BD twice daily, cART combination antiretroviral therapy, CVD cardiovascular disease, LSM liver stiffness measurement, OBT optimised background therapy

Trial objectives are show in Box 1. A sample size of n=30 per group would allow estimation of a difference in the Enhanced Liver Fibrosis (ELF) score of 1 point with 95% CI of 0.3-1.7, assuming an SD of 1.12 and an attrition rate of 33%.

Box 1. Trial objectives

Primary objective
Establish the acceptability and feasibility of conducting an RCT of add-on maraviroc versus OBT in HIV-NAFLD

Secondary objectives – evaluate changes in:
1. Hepatic fibrosis and fat
2. Lipids & glucose metabolism
3. Metabolic syndrome markers
4. HIV parameters
5. Quality of life
6. CT liver : spleen attenuation ratio (optional)

RESULTS

Of n=80 individuals referred for screening, 53 (66%) met eligibility criteria and enrolled. Baseline characteristics are shown in Table 1 and were broadly comparable between groups. In the MVC+OBT group, 5/23 (22%) individuals discontinued the study due to: ineligibility identified post randomisation, an Adverse Reaction (AR), pill burden or loss to follow up (LTFU) (n=2). In the OBT group, 4/30 (13%) discontinued: one died from COVID-19 and n=3 were LTFU. Primary outcomes measures are shown in Box 2 There were five ARs: worsening of restless legs, drowsiness with appetite loss, rash with vomiting, and dizziness (n=2). Two individuals with AR discontinued MVC, at 21 and 81 weeks. All ARs were of mild or moderate intensity and resolved Two SAEs were noted in the MVC+OBT group (pneumonia and gastro-oesophageal reflux disease) and four SAE in the OBT group: (fatal COVID-19, urinary retention from benign prostatic hyperplasia, suicidal ideation, listeria meningitis).

Box 2. Primary outcome measures

1. Acceptability of recruitment: 53/59, 90% [95%CI 79%,96%] > target of 50%
2. Monthly participant recruitment rate: 2.9 individuals / month > target of 2 / month
3. Participant retention, 44/53, 83% [95%CI 70%, 92%] > target of 65%
4. Data completeness: 96% > target of 80%
5. Adverse reactions: 5/23, 22% [95% CI 5%, 49%] > target of 10%
6. Adherence to maraviroc: 92% [SD=7%] > target of 90%

RESULTS

Table 1. Participant baseline characteristics

	MVC+OBT (N=23)		OBT (N=30)		Total (N=53)	
	Med/n	IQR/%	Med/n	IQR/%	Med/n	IQR/%
Age, years	51	38 to 59	55	49 to 61	54	47 to 60
Male	20	87%	27	90%	47	89%
White	19	83%	28	93%	47	89%
BMI, Kg/m^2	28	26 to 32	31	26 to 35	30	26 to 35
Waist circumference, cm	102	95 to 113	108	96 to 116	106	95 to 115
Systolic BP, mmHg	129	124 to 136	132	121 to 141	130	123 to 140
Duration HIV infection, years	16	12 to 23	14	9 to 22	15	11 to 22
CD4 count, cells/mm^3	702	546 to 1007	745	514 to 1055	702	545 to 1035
HbA1c, mmol/mol	38	32 to 42	39	35 to 45	38	33 to 43
ALT, U/L	45	31 to 62	44	29 to 69	44	31 to 69
GGT, U/L	45	33 to 97	41	26 to 58	42	30 to 72
Fasting LDL, mmol/L	2.8	2.3 to 3.3	2.8	1.8 to 3.1	2.8	2.1 to 3.3
Fasting HDL, mmol/L	1.2	1 to 1.5	1.1	0.9 to 1.2	1.1	0.9 to 1.3
Fasting TG, mmol/L	1.7	1.2 to 3	1.7	1.3 to 2.5	1.7	1.3 to 2.5
Metabolic syndrome	11	48%	16	53%	27	51%
Liver Stiffness, kPa	6.4	4.9 to 8.9	5.7	4.5 to 7.3	6.2	4.6 to 7.8
CAP score, dB/m	335	235 to 349	313	267 to 347	320	267 to 347
ELF score	9.2	8.5 to 9.5	9.0	8.7 to 9.6	9.1	8.6 to 9.6
INSTI-based cART	10	43%	18	60%	28	53%
PI-based cART	4	17%	4	13%	8	15%
TAF	5	22%	10	33%	15	28%

For secondary outcomes, changes were compared between groups from baseline to weeks 48 and 96 in clinical characteristics, including ALT, lipids, HbA1c, CD4 count, ELF, LSM and CAP scores. The 95% CI were generally wide, indicating relatively imprecise estimation of the between-group differences, due to the small sample size. In all cases, 95% CIs included zero, consistent with there being no differences between treatment groups, (See Table 2). Trends over time were mostly similar comparing treatment groups but with two differences. From baseline to week 96, decreases were seen in ALT (-8 IU/L) and LSM scores (-0.95kPa) for the MVC+OBT group versus increases in the OBT group (+4 IU/L and +0.65 kPa respectively). Consistent with this, CAP score improvements were greater in the MVC+OBT group (-59 dB/m versus -20 dB/m). However, 95% CIs were consistent with there being no differences. As only seven individuals completed the CT sub-study, CT results were excluded from the main analyses. For quality of life outcomes, 95% CIs were also wide for between-group comparisons, and included zero in all cases, consistent with there being no differences.

Table 2. Difference in change from baseline in metabolic and liver parameters for MVC+OBT vs OBT groups with bootstrapped 95% confidence intervals

	Week	No. of participants	Diff between groups in change from baseline	95% lower confidence limit	95% upper confidence limit
BMI, kg/m2	48	45	-0.2	-1.0	0.6
	96	45	-0.2	-0.8	0.4
Waist circumf., cm	48	43	2.7	-5.1	10.5
	96	42	1.3	-7.3	9.9
CD4 count, c/mm^3	48	45	69.8	-35.3	175.0
	96	44	-46.8	-134.7	41.4
HbA1c, mmol/mol	48	45	-2.3	-6.6	2.1
	96	45	2.5	-3.0	8.0
ALT, U/L	48	44	-5.7	-21.6	10.2
	96	45	0.5	-19.4	20.4
TG, mmol/L	48	44	0.7	-0.1	1.0
	96	46	-0.2	-1.0	0.6
LDL, mmol/L	48	40	0	-0.5	0.4
	96	41	0	-0.4	0.5
HDL: TC ratio	48	44	0.3	-0.6	1.4
	96	46	-0.3	-1.0	0.4
LSM, kPa	48	43	-1.7	-3.8	0.4
	96	41	-0.2	-2.0	1.6
CAP, dB/m	48	41	-15.1	-55.7	25.4
	96	39	-5.8	-41.0	29.5
ELF score	48	43	0.3	0	0.6
	96	42	0.1	-0.3	0.4

DISCUSSION

This feasibility study provides preliminary evidence of maraviroc safety amongst people with HIV-NAFLD who do not have cirrhosis, and acceptable recruitment, retention and adherence rates. Five of the six pre-specified primary outcome measure targets were met. The sixth measure, AR, exceeded the target but the 95% CI was wide and included the target value. All AR resolved, with no SARs.

We found no evidence of differences between the treatment groups in clinical outcomes, including liver fat and fibrosis scores. We did note decreases in ALT and LSM scores in the MVC+OBT versus increases in the OBT group, but 95% CIs were consistent with there being no difference, and the trial was not powered to evaluate treatment effects. In conclusion, an RCT to evaluate for the efficacy of add-on maraviroc in HIV-NAFLD is feasible and should include assessment of liver function and stiffness parameters.

The authors wish to thank the participants who generously took part in this trial. Please note that funding was from ViiV Healthcare: the funder had no role in trial set up, conduct, analyses or report writing.