Telmisartan to reduce insulin resistance in HIV-positive individuals on combination antiretroviral therapy: the TAILoR dose-ranging Phase II RCT

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Scientific summary

The TAILoR dose-ranging Phase II RCT

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Scientific summary

Background

Combination antiretroviral therapy (cART) is the mainstay of treatment for human immunodeficiency virus (HIV) and has dramatically improved the morbidity and mortality associated with HIV, turning it into a chronic disease. However, cART, together with the virus itself, can lead to various metabolic complications such as obesity, type 2 diabetes mellitus (T2DM) and an increased risk of cardiovascular disease (CVD). In the HIV DAD (Data collection on Adverse events of anti-HIV Drugs) cohort, patients with metabolic syndrome (MS) had a fourfold increase in the incidence of T2DM and a twofold to threefold increased risk of CVD. Long-term cART exposure also leads to an increased incidence of myocardial infarction, intima–media thickness and carotid lesions.

Insulin resistance, a key feature of MS, is central to cardiometabolic disease and is an important link between features of MS, obesity, dyslipidaemia, T2DM and CVD. The prevalence of insulin resistance in cART-treated patients infected with HIV ranges from 21% to 37%. Clinical interventions that arrest or reverse cART-associated insulin resistance represent a strategy to reduce the incidence of T2DM and CVD in patients infected with HIV. Insulin sensitisers such as thiazolidinediones and metformin have been investigated, but randomised clinical trials in patients infected with HIV have shown mixed results. Therefore, there is a need for novel clinical interventions with proven safety profiles that can reduce cART-induced insulin resistance in individuals infected with HIV.

The angiotensin II receptor blocker telmisartan also has partial agonist properties at the peroxisome proliferator-activated receptor-γ, an important regulator of adipocyte function. Prospective randomised clinical trials in patients with diabetes mellitus, and those with MS, have shown that telmisartan significantly reduces insulin resistance. Telmisartan also has wide-ranging beneficial effects on various components of the MS: it results in reductions in fasting glucose, insulin, glycosylated haemoglobin, homeostatic model assessment of insulin resistance (HOMA-IR); increases adiponectin; improves lipid parameters; and reduces visceral fat. This study, and others, has shown that telmisartan partially reverses the antiadipogenic effects of antiretrovirals in vitro. This in vitro study also showed a non-monotone relationship of telmisartan on adiponectin and lipin 1 secretion. However, whether or not telmisartan would be clinically efficacious in reducing insulin resistance in cART-treated patients infected with HIV has not been assessed. This trial, therefore, was designed to address this important question, coupled with an assessment of the dose–response relationship of telmisartan in vivo.

Objectives

Primary objective

To determine the effect of telmisartan on insulin resistance in individuals infected with HIV on cART using HOMA-IR as a measurable, validated surrogate marker of insulin resistance.

Secondary objectives

- To define the optimal dose of telmisartan that can significantly reduce insulin resistance.
- To measure HOMA-IR values at baseline (T0) and at 12, 24 and 48 weeks to provide data on time to, and sustainability of, any reduction in HOMA-IR.
- To utilise alternative indices of insulin resistance such as Quantitative Insulin Sensitivity Check Index (QUICKI) and revised QUICKI to determine the effect of telmisartan on insulin resistance.

- To mechanistically evaluate whether or not telmisartan modulates the plasma concentrations of both beneficial (adiponectin) and adverse [leptin, resistin, tumour necrosis factor alpha (TNF-α), high-sensitivity C-reactive protein (hs-CRP)] biomarkers, which may help in further stratifying telmisartan therapy in the future.
- To determine whether or not telmisartan improves general lipid homeostasis and reduces visceral fat accumulation in individuals infected with HIV on cART over a 24-week period.
- To determine, in a substudy, whether or not proton magnetic resonance spectroscopy (^{1}H-MRS)-assessed intrahepatic and intramyocellular triglyceride content, markers of hepatic steatosis and insulin resistance, respectively, are reduced by telmisartan therapy.
- To determine whether or not telmisartan has an effect on urinary biomarkers [albumin-to-creatinine ratio (ACR), neutrophil gelatinase-associated lipocalin (NGAL)] of renal injury in individuals infected with HIV on cART.
- To evaluate the tolerability of telmisartan in this patient group.

Methods

Trial design

TAILoR was a multicentre, randomised open-labelled study with an adaptive design. The adaptive design consisted of two stages. In stage 1, eligible patients were randomised on a 1 : 1 : 1 : 1 basis to either no treatment or 20, 40 or 80 mg of telmisartan once daily. The duration of study treatment was a maximum of 48 weeks, with follow-up visits at 12, 24, and 48 weeks. An interim analysis was performed when half of the planned maximum number of patients had been followed up for at least 24 weeks. A subset of patients in the main study took part in the magnetic resonance imaging (MRI) substudy over 24 weeks.

Participants

TAILoR participants were adults (aged ≥ 18 years) with documented HIV infection who had been receiving a stable cART for at least 6 months prior to randomisation. The backbone of therapy was based on nucleotide reverse transcriptase inhibitors, raltegravir or maraviroc, and patients should have been on a boosted protease inhibitor (lopinavir/ritonavir, atazanavir/ritonavir, darunavir/ritonavir, fosamprenavir/ritonavir, saquinavir/ritonavir) and/or efavirenz, rilpivirine or etravirine for at least 6 months.

Patients were excluded if they were diabetic, had low blood pressure, renal disease, untreated renal artery stenosis, cholestasis, biliary obstructive disorders or severe hepatic impairment, active chronic hepatitis C infection, were on/had been on hormone therapy, anabolics and insulin sensitisers, or any other product likely to influence insulin sensitivity within 6 months preceding randomisation, and/or were on other angiotensin receptor blockers, angiotensin-converting enzyme inhibitors or direct renin inhibitors within 4 weeks preceding randomisation. Patients with suspected poor compliance, pregnant or lactating women, women of childbearing age unless using reliable contraception, and those co-enrolled into other drug trials were also excluded.

Study settings

The trial was conducted in 19 UK sexual health clinics and/or HIV treatment centres from March 2013 to July 2015.

Interventions

All patients were randomised to either no treatment or telmisartan (20-, 40-, or 80-mg doses taken once daily) depending on treatment allocation. The duration of the treatment was 48 weeks. Patients were asked to complete treatment diaries, detailing compliance.

Sample collection

Blood and urine were collected at four time points during the trial (baseline, 12, 24 and 48 weeks/end of trial). The samples were shipped on dry ice and stored in a category 2 laboratory equipped to handle and store infectious samples.

Laboratory measurements

The objective measure of efficacy of trial treatment on insulin resistance was provided by a comparison of HOMA-IR values, a validated marker of insulin resistance, for the baseline and weeks 12, 24 and 48. Two other surrogate measures of insulin sensitivity, QUICKI and revised QUICKI using serum levels of non-esterified fatty acids, were also assessed.

Other assessments carried out were plasma lipid profile (cholesterol, triglycerides, high- and low-density lipoprotein cholesterol), plasma biomarkers of metabolic function (adiponectin, leptin, TNF-α, resistin and interleukin 8) and renal markers (ACR, NGAL).

Magnetic resonance imaging substudy

Magnetic resonance imaging of total body adipose content was carried out using T1-weighted MRI scans in 10 overlapping blocks of 1-cm slices with 1-cm gap, in upper and lower halves of the body separately. A validated semiautomatic program was used to segment and analyse the images into total body subcutaneous, total internal, subcutaneous abdominal and intra-abdominal adipose tissue volumes.

Pharmacovigilance

Adverse events/reactions for the TAILoR trial were monitored from the time of consent until 7 days after the patient had taken the final dose of telmisartan.

Statistical considerations

Sample size

The original maximum total sample size of the study was 336 patients. The primary response from each patient was the difference between the HOMA-IR score at 24 weeks and the baseline HOMA-IR score (so that negative values indicate improvement). The design had been constructed under the assumption that for all patients this response is normally distributed with a common standard deviation, σ. The sample size calculation was based on a one-sided type I error of 5% and a power of 90%. To fix a power requirement, effect sizes were specified in terms of the percentage chance of a patient on active treatment achieving a greater reduction in HOMA-IR score than a patient on the control arm; as such, the specification did not require knowledge of the value of the common standard deviation σ. The critical values for recommending that a treatment was taken to further testing at the interim and final analyses (–2.782 and –2.086) had been chosen to guarantee these properties that pertain to the whole two-stage testing procedure. The study was designed to recruit additional patients to ensure that the target number of 24-week responses was achieved in the presence of an anticipated 10% dropout rate (which increased the sample size to 370 patients).

Sample size for the substudy 1 (magnetic resonance imaging/proton magnetic resonance spectroscopy)

A sample size of 10 patients per group was expected to provide sufficient data for a reliable estimate of the within-group variance (sample size was increased to 12 to account for 10% dropout).

Interim analysis and stopping guidelines

The interim analysis was scheduled to take place once the 24-week change in HOMA-IR score was available for at least 42 patients in each arm ($n = 168$, which was half of the planned maximum of 336 patients). The sample standard deviation pooled across all four arms was used to construct test statistics expressing the advantage of each of the three active treatments over the control arm.

Statistical methods

Primary outcome analysis

In order to satisfy the primary objective, we evaluated three different doses against control in the first stage of the study and conducted an interim analysis that allowed ineffective doses to be eliminated quickly while a dose showing a reduction in HOMA-IR was taken forward. The smallest of these test statistics was to be compared with the interim critical value (–2.782). Observing a test statistic below this value corresponded to a significant improvement in HOMA-IR score for the corresponding dose over control and would have led to this dose being immediately taken forward for further study, and to the trial being stopped. Any dose corresponding to a positive test statistic would have been dropped, and if all doses were dropped the trial would also have been stopped. If some reduction in HOMA-IR over control was detected for at least one of the active doses (i.e. test statistic between 0 and –2.782), then the study continued after the interim analysis. At the final analysis, if the smallest comparative test statistic was below the final critical value (–2.086) then this dose would be recommended for further study. Adjustments were made to allow for any discrepancies between target and actual sample sizes while still preserving the one-sided type I error rate at 0.05.

Secondary outcome analysis

Biomarker analysis

To explore the secondary objective of identifying longitudinal change in the expression of biomarkers in telmisartan-treated arm(s) in comparison with controls, joint models were used to fully exploit the serial nature of these outcomes accounting for informative loss to follow-up and missingness.

Analysis of changes in body fat redistribution and intrahepatic and intramyocellular lipid content

The change in visceral, liver and limb fat in 24 weeks was compared across the three treatment groups and controls using multiple linear regression.

Trial procedures

The trial was managed by the Clinical Trials Research Centre at the University of Liverpool. It was conducted in accordance with the European Clinical Trials Directive (European Commission. *Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001*. Brussels: European Commission; 2001), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)'s Good Clinical Practice Guidelines [ICH. *ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6(R1)*. 1996. URL: www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf (accessed 24 September 2018)], the Declaration of Helsinki (World Medical Association. Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013;**310**:2191–4), the NHS Research governance framework [NHS Health Research Authority. *UK Policy Framework for Health and Social Care Research. Version 3.3*. 2017. URL: www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/uk-policy-framework-health-social-care-research/ (accessed 24 September 2018)] and the Medicines for Human Use (Clinical Trials) Regulations 2004 [Great Britain. *The Medicines for Human Use (Clinical Trials) Regulations 2004*. London: The Stationery Office; 2004]. Three committees oversaw the conduct of the trial: the Trial Management Group, the Trial Steering Committee and the Independent Data and Safety Monitoring Committee. Patient representatives were identified early in the trial and were involved in the overseeing of the trial. One representative sat on the Trial Steering Committee and one on the Trial Management Group.

Results

Screening and participant flow

In total, 1950 patients were screened at the participating centres over the duration of the trial.

Baseline data

The baseline characteristics were balanced across treatment arms. The study participants were predominantly male.

Primary outcome results

Interim analysis

The *t*-statistic for arms B (20 mg of telmisartan) and C (40 mg of telmisartan) showed a positive value (i.e. ≥ 0) which implied that there was no reduction in the HOMA-IR over control (arm A) and, therefore, these active dose arms were dropped from the second stage. As some improvement over control was detected for arm D (80 mg of telmisartan) (i.e. the *t*-statistic was between 0 and –2.782), this arm was selected to progress into the second stage of the study and the patients were thereafter randomised between arm D and the control group (arm A).

Final analysis

Given that the test statistic was not smaller than the critical value of –2.086 [estimated effect 0.007, standard error (SE) 0.106], it was concluded that there was no significant difference in HOMA-IR between arms D and A.

Secondary outcome results

Alternative indices of insulin resistance (Quantitative Insulin Sensitivity Check and revised Quantitative Insulin Sensitivity Check)

For QUICKI (0.001, SE 0.001) and revised QUICKI (0.002, SE 0.002), the test statistic was not smaller than the critical value (–2.086), suggesting no difference between arms A and D.

Longitudinal analysis of Homeostatic Model Assessment of Insulin Resistance, Quantitative Insulin Sensitivity Check and revised Quantitative Insulin Sensitivity Check

There was no significant difference in HOMA-IR and QUICKI between the treatment and control arms over a period of 48 weeks. However, the treatment effect of arm D compared with arm A for the longitudinal revised QUICKI was marginally significant [0.004, 95% confidence interval (CI) 0.000 to 0.008; $p = 0.05$], suggesting that telmisartan (80 mg) led to a small reduction in insulin resistance over a period of 48 weeks.

Longitudinal analysis of lipid profiles and plasma biomarkers

There were no significant differences between the treatment arm and the control arm with any of the lipid markers over a period of 48 weeks. None of the plasma biomarkers, apart from hs-CRP, showed a significant change (–0.222, 95% CI –0.433 to –0.011; $p = 0.04$) over time between the control and the telmisartan (80-mg) treatment arm.

Substudy 1: magnetic resonance imaging

No statistically significant differences were observed in internal visceral fat or intramyocellular triglyceride content in the soleus and tibialis anterior at 24 weeks between the treatment group (80 mg) and the control group ($p > 0.05$). However, a statistically significant difference in the intrahepatic triglyceride content was observed at 24 weeks between arm D and the control group (arm A) (1.714, 95% CI –2.787 to –0.642; $p = 0.005$).

Substudy 2: urine/renal biomarkers

The estimated treatment effects [arm D (80 mg) compared with arm A (control)] on NGAL were not significant in any of the tertile subgroups tested. A telmisartan dose of 80 mg significantly reduced ACR for the subgroup with albumin excretion of > 3 mg/mmol (–0.665, 95% CI –1.31 to –0.019; $p = 0.04$).

Safety data analysis

Diarrhoea, fatigue, dizziness and pruritus were the most common adverse reactions, observed in > 2% of patients. There was no evidence of a difference in the percentage of serious adverse events between the telmisartan-treated arms and the control arm ($p = 0.8$).

Conclusions

Using a novel adaptive design, we demonstrated that there was no significant effect of telmisartan (80 mg) on the primary outcome measure (HOMA-IR) and some secondary outcomes (plasma lipids and adipokines). Telmisartan did lead to favourable changes of the secondary longitudinal outcome measures: revised QUICKI, hs-CRP, hepatic fat accumulation and urinary albumin excretion. Although these changes are biologically plausible and consistent with the literature, whether or not this would translate into improvements in clinical outcomes in patients infected with HIV on cART is unclear. Taken collectively, our findings showed that telmisartan did not reduce insulin resistance in patients infected with HIV on antiretrovirals.

Trial registration

This trial is registered as ISRCTN51069819.

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