

Project Title:	A randomised controlled trial of losartan as an anti-fibrotic agent in non-alcoholic steatohepatitis
Project Ref:	08-43-15
Cost:	£941,463
Lead Applicant & Institution:	Professor Christopher Day Faculty of Medical Sciences Newcastle University
Start Date:	Anticipated 1 May 2010
Plain English Summary:	<p>Liver scarring (fibrosis) is the end result of almost every chronic liver disease. Ultimately this scarring can result in cirrhosis which carries with it the risks of liver cancer, liver failure and death. Treatment for fibrosis is entirely aimed at prevention. In non-alcoholic fatty liver disease, this prevention is based around largely ineffective lifestyle measures. Any treatment that could reverse or even slow down fibrosis would have major implications for the management of these patients. Indeed, the development of agents that halted, or even slowed down, progression would be very useful in liver disease in general.</p> <p>The mechanisms behind the development of fibrosis have become increasingly clear over the last few years. It appears that, in addition to its established role in the control of blood pressure, the hormone angiotensin II has a central role in the development of fibrosis. It does this through stimulating the scar-producing cells (stellate cells) to grow and produce scar tissue. Some initial studies have shown that blocking this hormone can induce the death of these cells and prevent fibrosis. Angiotensin II blockers, such as losartan were initially developed for the treatment of high blood pressure (hypertension). More recently preliminary studies treating patients with liver disease with losartan have been very promising. This treatment may even lead to a reduction in the amount of scar tissue; something that up until recently had been thought impossible.</p> <p>The aim of this trial is to determine whether losartan can prevent the progression of, halt or even reverse fibrosis in non alcoholic fatty liver disease. We will compare losartan with placebo (a tablet or capsule that has no active effect) over a period of 24 months. The effect of the treatment will be determined by a variety of tests that determine the severity of fibrosis. These include liver scan, blood tests and the analysis of liver biopsies. In addition, laboratory work will be done to test the theories of how angiotensin II promotes fibrosis.</p> <p>Should losartan have a significant effect on fibrosis development it would become a safe and cheap treatment for many patients. It would reduce the rate of progression to end-stage liver disease and reduce the number of</p>

	<p>patients with liver failure and liver cancer. In addition, it would limit the numbers of patients that progressed to require transplantation. If it has an effect on reducing fibrosis it may even be used to "heal" cirrhosis and give the only realistic hope of cure without transplantation to these patients.</p>
Abstract:	<p><u>Design:</u> Two-arm, parallel group, double blind, randomised, placebo-controlled trial</p> <p><u>Setting:</u> Five tertiary referral centres for the management of liver disease: Freeman Hospital, Newcastle upon Tyne (lead centre), Edinburgh, Nottingham, Birmingham and London (St. Mary's).</p> <p><u>Target population:</u> Adults (aged 18+), with steatohepatitis and fibrosis, resulting from non alcoholic fatty liver disease. Intervention: Angiotensin receptor blocker (Losartan) at a dose of 50 mg once a day vs. matched placebo for 24 months.</p> <p><u>Measurement of outcomes and duration of follow-up</u> The primary outcome will be change in Kleiner fibrosis score. Duration of treatment will be 24 months, with biopsies at month 0 (pre-treatment) and month 24 (end-of-study). Secondary outcomes will be a change in radiological (fibroscan) and serological (ELF) markers of fibrosis; both of which have been validated against the histological gold-standard. A further secondary outcome is the change in NAFLD activity score (NAS) from baseline. This will be determined from trial entry and end-of-study liver biopsies.</p> <p><u>Sample size:</u> A total 170 patients will be required.</p> <p><u>Project timetable</u> The study is planned for 42 months.</p>
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