New drug achieves significant additional cholesterol-lowering in people with inherited high cholesterol on statins

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Evolocumab, an injected form of a new class of drugs called PCSK9 inhibitors[1], is highly effective at reducing low-density lipoprotein (LDL) or "bad cholesterol" levels with few side effects in people with familial hypercholesterolaemia (FH), an inherited condition that causes extremely high cholesterol and high risk of cardiovascular disease at an early age.

Published in *The Lancet*, the results of two of the largest global randomised trials ever undertaken in this field found that evolocumab rapidly cut levels of LDL cholesterol by on average 60% more than those given a placebo in patients with heterozygous FH (a common form of the disease), and by 31% more than placebo in patients with the much rarer homozygous form.

"Despite intensive cholesterol-lowering therapies such as statins, most patients with FH do not achieve LDL cholesterol targets recommended to prevent cardiovascular disease. However, currently we have no alternative or additional drug treatment with strong LDL-lowering ability and good tolerability", explains lead investigator Professor Frederick Raal, Director of the Carbohydrate and Lipid Metabolism Research Unit at the University of Witwatersrand, Johannesburg, South Africa.

FH is caused mainly by genetic defects in the LDL receptor gene that impairs the ability of the liver to remove LDL cholesterol from the blood. In most cases the defective gene is inherited from one parent causing heterozygous FH that affects between 1 in 250 and 1 in 300 people worldwide—making it the most common hereditary disorder in humans. More than 3 million people are estimated to have the disorder in the USA and Europe alone. Homozygous FH means that the person has inherited a mutated copy of the gene from both parents, and is a much more severe form that affects roughly 1 in every 500 000 to a million people.

The RUTHERFORD-2 trial recruited 331 patients aged 18 to 80 years old with heterozygous FH who were already taking high-dose statins with or without ezetimibe[2] from 39 sites in Australia, Asia, Europe, New Zealand, North America, and South Africa. Participants were randomly assigned to receive one of two doses of evolocumab (140mg every 2 weeks or 420mg monthly), or matching placebo for 12 weeks. Evolocumab was strikingly more effective at reducing LDL cholesterol than placebo. At 12 weeks, both dosage regimens of evolocumab produced rapid 60% reductions in LDL cholesterol levels compared with placebo. What is more, over 60% of patients given evolocumab achieved recommended LDL cholesterol levels of lower than 1.8 mmol/L. Evolocumab was well tolerated with comparable rates of adverse event rates to placebo.

In the TESLA Part B trial, 49 patients aged 12 years and older with homozygous FH from 10 countries in North America, Europe, the Middle East, and South Africa were randomly assigned to monthly injections of evolocumab 420 mg or matching placebo for 12 weeks on top of high-dose statins often in combination with ezetimibe. Compared with placebo, evolocumab reduced LDL cholesterol by on average 31%, and by 41% in patients with at least one defective LDL receptor mutation. Evolocumab was well tolerated with no serious adverse events reported.

According to co-lead author Professor Evan Stein, from the Metabolic and Atherosclerosis Research Center, Cincinnati, USA, "Our results indicate that evolocumab achieves similar cholesterol reductions but with a more rapid onset of action and fewer side effects than two drugs recently approved as orphan

therapies for homozygous FH—mipomersen and lomitapide"

Writing in a linked Comment, Professor Raul Santos from the University of Sao Paulo Medical School Hospital, Sao Paulo, Brazil and Professor Gerald Watts from the University of Western Australia, Perth, Australia say, "If proven to be safe and efficacious in the long term, as well as cost effective, PCSK9 monoclonal antibodies might be the best standard of care for many patients with severe forms of familial hypercholesterolaemia ...However, the wider applications of PCSK9 monoclonal antibodies as an additional therapy to statins will depend on the results of large clinical outcome trials, such as ODYSSEY with alirocumab, FOURIER with evolocumab, and SPIRE-1 and SPIRE-2 with bococizumab, that are underway in patients at high risk of cardiovascular disease."

More information: [1] Evolocumab works by inhibiting PCSK9 which leads to an increase in the liver's ability to clear LDL cholesterol from the blood.

[2] Ezetimibe is a cholesterol-absorption inhibitor. It works in the small intestine by inhibiting the absorption of cholesterol into the body from ingested food, which leads to a reduction in blood cholesterol levels.

RUTHERFORD-2 www.thelancet.com/journals/lan … (14)61399-4/abstract

TESLA Part B www.thelancet.com/journals/lan … (14)61374-X/abstract

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