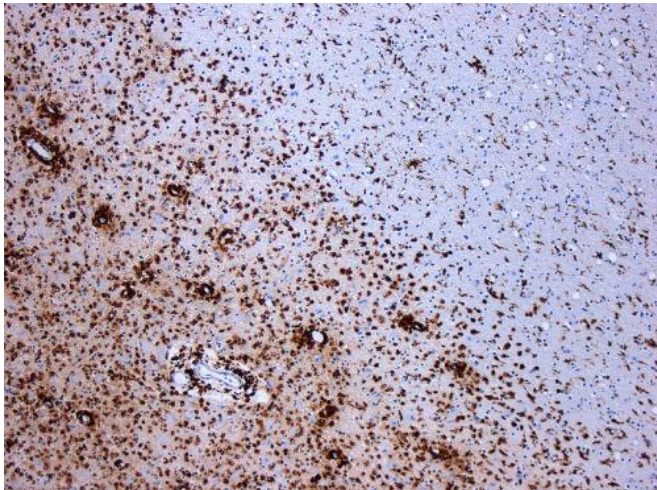


Statins' potential to treat multiple sclerosis unrelated to lowering cholesterol

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Demyelination by MS. The CD68 colored tissue shows several macrophages in the area of the lesion. Original scale 1:100. Credit: Marvin 101/Wikipedia

The widely prescribed statin, simvastatin, can medically help patients with secondary progressive Multiple Sclerosis (SPMS)—for reasons that might be unrelated to the drug's intended cholesterol lowering effects, a UCL study has found.

"Although this study cannot provide a final answer as to what exactly is the reason for the success of statins in progressive MS, it directs future researchers toward certain pathways," said lead author, Dr. Arman Eshaghi (UCL Queen Square Institute of Neurology).

"This paves the way to find better drug targets for an incurable disease such as MS."

MS affects over 100,000 people in the UK, and most expect to develop a progressive form of the condition. It causes problems with how people walk, move, see, think, and feel. There is currently no cure for MS and little effective treatment for

SPMS.

Primary research

Researchers used data from the UCL-led Phase 2 MS-STAT trial, which saw 140 people with SPMS either take a high dose of simvastatin (80mg a day) or a placebo for two years. Participants were aged 18-65 and had Expanded Disability Status Scale (EDSS) scores of between 4 and 6.5.

Throughout the trial, brain volume was assessed using MRI brain scans, levels of disability were assessed using the EDSS and serum [cholesterol](#) levels were measured, and participants completed several questionnaires that examined the impact of MS on their daily lives.

In the group taking simvastatin, [brain volume](#) loss was 43% less compared to those taking placebo. Smaller but still significant effects on two of the disability measures were also found, there was a slower change in EDSS (disability levels) and improved scores on a questionnaire which measures the impact of MS on daily life.

While this study showed simvastatin had a [positive effect](#) on delaying disability worsening and slowing brain atrophy (shrinkage) of people with SPMS, it was not entirely certain what the cause of that benefit was.

Latest study using computational models

In this study, published in *Proceedings of the National Academy of Sciences (PNAS)*, researchers reanalysed the MS-STAT trial data and modelled hypothesised causal associations by which simvastatin leads to changes in brain atrophy, clinical and cognitive outcome measures, either directly or indirectly via changes in a patient's peripheral cholesterol level.

The study tested the hypothesis that the reduction

in cholesterol levels was the cause of the positive impact simvastatin had on brain atrophy and on disability, against the alternative hypothesis that simvastatin effects were independent of peripheral cholesterol level.

Two computational models were developed. The first was a cholesterol-mediated model, in which the effects of simvastatin on clinical measures (both physical and cognitive) and brain atrophy are brought about by changes in cholesterol. The second was a cholesterol-independent model, in which simvastatin has a direct effect on the clinical and MRI outcome measures, independent of its effect on serum cholesterol levels.

Researchers tested both models using statistical analyses designed to answer causal questions, such as, is the reason that simvastatin helps reduce brain shrinkage the same as the reason it reduces cholesterol in the blood?

Results showed that simvastatin's effect on clinical outcomes and brain atrophy were largely independent of cholesterol.

Dr. Eshaghi said: "Statins are naturally occurring, produced by some fungi, meaning that unlike most drugs that are designed for specific targets, they have (still after two decades of use in heart diseases) several unknown effects, and that is why this study is so important.

"My study tells us that statins help patients with MS for reasons different from how they help people lower their cholesterol. For example, statins can modulate other elements that are produced in the pathways before cholesterol, but have indirect effects on immune system."

Simvastatin is currently widely used to treat high cholesterol, and can be taken daily as an oral tablet. Statins have been shown to have an effect on the nervous system in protecting the nerves, and can also act as an anti-inflammatory treatment.

Professor Alan Thompson, Dean of the UCL Faculty of Brain Sciences and Chair of the Scientific Steering Committee of the Progressive MS Alliance, said: "Finding new and effective

treatments for progressive MS is one of the key challenges facing the MS community and further advances will require a better understanding of underlying mechanisms.

"This study provides interesting and important insights into such mechanisms."

This study was carried out with researchers from the University of Cambridge and Imperial College London and was funded by National Institute for Health Research Biomedical Research Centre, The Engineering and Physical Sciences Research Council (EPSRC), the European Union's Horizon 2020 Research and Innovation Programme, Medical Research Council, and Wellcome Trust.

Phase 3 trial

In September last year the biggest ever trial SPMS in the UK was launched, led by Professor Jeremy Chataway (UCL Queen Square Institute of Neurology and National Hospital for Neurology and Neurosurgery).

With around 30 sites across the UK and Ireland, the MS-STAT2 trial involves 1,180 people with SPMS. Over 400 participants are currently in trial.

Co-funded by the MS Society, MS-STAT2 is the final stage trial of the drug treatment simvastatin for SPMS. This Phase 3 study will confirm whether simvastatin could become amongst the first drugs to slow or stop disability progression for this form of the condition, offering new hope to thousands.

"Simvastatin is one of the most promising treatment prospects for secondary progressive MS in our lifetime. People with this form of the condition have been waiting decades for a drug that works, which is why there's such excitement around being able to start the trial," said Professor Chataway, who is leading the trial and is a co-author on the *PNAS* paper.

"While it's still early days, we believe [simvastatin](#) could change lives."

More information: Arman Eshaghi et al, Applying causal models to explore the mechanism of action

of simvastatin in progressive multiple sclerosis,
Proceedings of the National Academy of Sciences
(2019). DOI: [10.1073/pnas.1818978116](https://doi.org/10.1073/pnas.1818978116)

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