# Combining statins with interferon beta in multiple sclerosis: think twice, it might not be all right

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Since the finding that cholesterol-lowering statins could induce T-cell-mediated immune modulation and reverse paralysis in mice with experimental autoimmune encephalomyelitis (EAE),[1] there has been substantial interest in whether this class of drugs is beneficial in multiple sclerosis. One question that has not been answered is whether a statin used alone is beneficial; more energy has been devoted to establishing whether statins can provide added benefit when combined with interferon beta, the most commonly prescribed class of drug in multiple sclerosis. Results from trials have been mixed.[2–5] Although one study showed that the combination of a statin with interferon beta was antagonistic,[2] other small studies have suggested that there could be a benefit.[4,5]

In this issue of *The Lancet Neurology*, Per Soelberg Sorensen and colleagues[6] tested whether oral simvastatin could augment the benefit of intramuscular interferon beta-1a. 307 treatment-naive patients with relapsing-remitting multiple sclerosis were enrolled in the SIMCOMBIN trial, the largest study to date evaluating the combination of a statin with interferon beta in multiple sclerosis. After a 3-month run-in period with weekly intramuscular interferon beta-1a, patients were randomly assigned to receive simvastatin 80 mg (n=151) or placebo (n=156) in addition to interferon beta, then followed up for clinical exacerbations and development of demyelinating lesions on brain MRI for 1–3 years. Although the combination of simvastatin and interferon beta was tolerated, no significant difference was reported at 12 months in annualised relapse rate (the primary endpoint) or in development of new or enlarging T2 brain MRI lesions. Not only was there a lack of benefit, but the non-significant suggestion of better results in the placebo group again raised concern that there could be antagonism when a statin and interferon beta are combined in multiple sclerosis treatment.

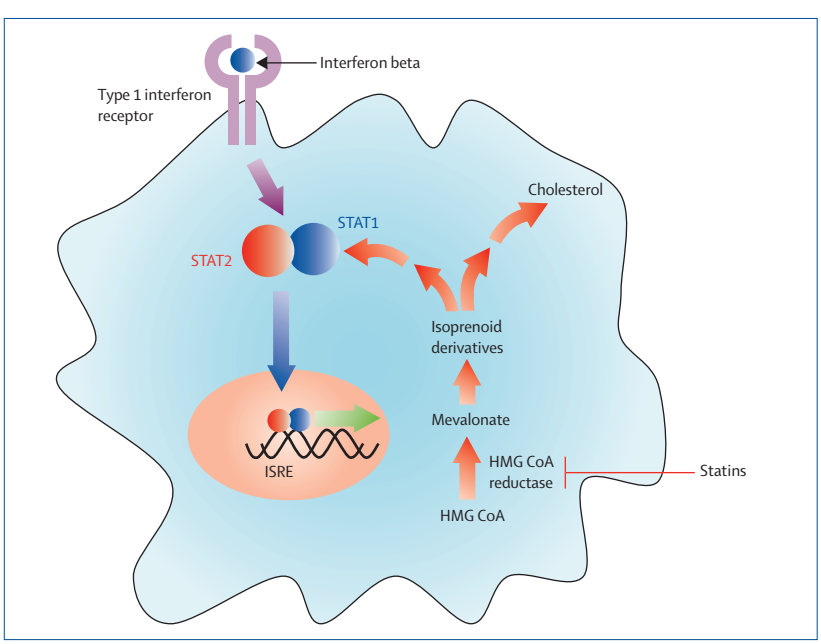


***Figure:*** **A molecular intersection at which statins might oppose interferon beta**
Binding of interferon beta to the cell surface type 1 interferon receptor leads to activation (phosphorylation) of the signal transducers and activators of transcription (STAT) 1 and STAT2, which then form heterodimers that enter the nucleus; in the nucleus, they bind the interferon stimulating response element (ISRE) and activate transcription of genes involved in immune modulation, antiviral responses, and antiproliferative responses. Statins passively enter cells and bind to their target, HMG CoA reductase, inhibiting the generation of mevalonate and its isoprenoid derivatives that serve as building blocks in cholesterol synthesis and modify signalling proteins. Statins can therefore inhibit expression or activation of STAT1, providing a focus for potential antagonism between interferon beta and statins.

Interferon beta binds to the type 1 interferon receptor, which is expressed on nearly all cells; this binding leads to activation of the signal transducers and activators of transcription (STAT) 1 and STAT2, the initial steps in the biochemical cascade leading to immune activation and regulation by type 1 interferons (figure). By inhibiting HMG CoA reductase, statins inhibit synthesis of molecular intermediates and so can block the activation of STAT1. Thus, opposing effects on STAT1 represent one point for potential antagonism. Although the combination of an interferon beta and a statin was not studied in vivo before testing in clinical trials, when tested in EAE, statins have increased the activity of other agents.[7,8] For example, atorvastatin increased the activity of glatiramer acetate, providing support for testing of this combination in multiple sclerosis. Interestingly, glatiramer acetate, like statins, inhibits STAT1 activation in myeloid cells.[9]

Clinical studies in multiple sclerosis have now tested different statins and preparations of interferon beta in combination. Just as individual interferon beta preparations differ in pharmacological characteristics, statins vary in their capability to reduce cholesterol and might differ in their potential immune modulatory

capabilities. Thus, each combination might not be the same. Antagonism was reported when atorvastatin, a potent statin, was tested with high-dose subcutaneous interferon beta-1a.[2] When simvastatin, which does not reduce cholesterol as efficiently as atorvastatin, was tested in combination with low-dose intramuscular interferon beta in the SIMCOMBIN study, no benefit was noted. Of the studies that have tested whether a statin should be combined with interferon beta, SIMCOMBIN is the only one to yield class 1 evidence. The investigators concluded that the combination of interferon beta and simvastatin should not be used as a treatment for relapsing-remitting multiple sclerosis.

We are now beginning to learn in whom interferon beta works and in whom it could actually worsen disease.[2] We are starting to unravel who might be a responder and who will be a non-responder to various treatments for relapsing-remitting multiple sclerosis, by use of predictive biomarkers[7] and characteristic patterns on imaging.[10] As predictive medicine becomes a standard for choice of drugs, examination of potential synergies will be worthwhile, to see whether inexpensive drugs approved for other conditions can improve efficacy of drugs for multiple sclerosis in responder populations. Such combinations of drugs can then be validated in preclinical experimental models before further clinical trials.[7,10] One ought to be careful when combining treatments in multiple sclerosis. In view of the lack of benefit and the potential for antagonism, one might want to think twice before adding a statin to interferon beta in multiple sclerosis treatment.

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# Genetics of intracerebral haemorrhage: a tsunami effect of *APOE* ε2 genotype on brain bleeding size?

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More than 2 million people worldwide have an intracerebral haemorrhage (ICH) every year and a third die within 1 month. However, no standardised work up for detection of the underlying causes of ICH exists, and the evidence for medical or surgical therapeutic interventions is limited.[1] Prevention strategies are needed, not least because ICH has a clear heritability, and management of this disease might be improved if genes that predict risk are discovered.[2]

The International Stroke Genetics Consortium has previously contributed to the topic by confirming an independent association of *APOE* ε2 and ε4 genotypes with the risk of lobar ICH in a large cohort of 2189 patients with ICH and 4041 controls.[3] The same core group has now assessed how factors that influence disease onset, such as *APOE*, might affect disease progression, and in this issue of *The Lancet Neurology* the Consortium reports an association between *APOE* genotypes and ICH volume.[4]

The authors should be congratulated for the collaborative effort that allowed them to do a candidate gene-association study in 865 patients with ICH of European ancestry, with replication in 946 European