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# Simvastatin as add-on therapy to interferon β-1a for relapsing-remitting multiple sclerosis (SIMCOMBIN study): a placebo-controlled randomised phase 4 trial.

Sorensen PS[1], Lycke J, Erälinna JP, Edland A, Wu X, Frederiksen JL, Oturai A, Malmeström C, Stenager E, Sellebjerg F, Sondergaard HB; SIMCOMBIN study investigators.

## Collaborators (47)

Soelberg Sorensen P, Lycke J, Erälinna JP, Edland A, Hillert J, Wilhelmsen L, Fazekas F, Oturai A, Jensen MB, Frederiksen J, Stenager E, Petersen T, Ravnborg M, Madsen C, Sivertsen B, Koch-Henriksen N, Walentin F, Nilsson P, Svenningsson A, Johansson R, Vrethem M, Landtblom AM, Olsson T, Alonso-Magdalena L, Martin C, Svensson L, Carlström C, Morsund ÅH, Mygland Å, Dueland AN, Celius E, Schüler S, Myhr KM, Schepel J, Bjørnstad B, Fahre E, Elovaara I, Soilu-Hänninen M, Multanen J, Koivisto K, Färkkilä M, Hallikainen M, Pirttilä T, Kinnunen E, Keskinarkaus I, Reunanen M, Sarasoja T.

## Author information

- [1]Danish Multiple Sclerosis Center, Department of Neurology, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark. pss@rh.dk

## Abstract

### BACKGROUND:

Treatment of relapsing-remitting multiple sclerosis with interferon beta is only partly effective. We aimed to establish whether add-on of simvastatin, a statin with anti-inflammatory properties, improves this efficacy.

### METHODS:

We enrolled treatment-naive patients with relapsing-remitting multiple sclerosis in a multicentre, placebo-controlled, double-blind, randomised, parallel-group trial of simvastatin (80 mg daily) as add-on treatment to intramuscular interferon beta-1a (30 μg weekly). After starting treatment with interferon beta, patients were randomly assigned (in computer-generated blocks of four patients) to simvastatin 80 mg per day or placebo for 1-3 years. Patients and treating and evaluating physicians were masked to treatment allocation. The primary outcome measure was annual rate of documented relapses; analysis was by intention to treat. This trial is registered at ClinicalTrials.gov, NCT00492765.

### FINDINGS:

We randomly assigned 307 patients to interferon beta plus simvastatin (n=151) or plus placebo (n=156). Annual rate of documented relapses was 0·19 (95% CI 0·13 to 0·28) in the simvastatin group and 0·14 (95% CI 0·09 to 0·23) in the placebo group (absolute difference 0·059, 95% CI -0·21 to 0·09; p=0·35). Time to first documented relapse (20th percentile) was 18·1 months in patients on simvastatin and 21·5 months in those on placebo (hazard ratio 1·21, 95% CI 0·74 to 1·99; p=0·51). Mean number of new or enlarging T2 lesions was 2·96 in the simvastatin group and 2·52 in the placebo group (ratio of new lesions, 1·17, 95% CI 8·89 to 1·55; p=0·25). Eight (6%) patients on simvastatin and 17 (13%) on placebo had no disease activity (odds ratio 0·42, 95% CI 0·17 to 1·00; p=0·05). No unexpected adverse events

were seen. Generally, adverse events were mild and there were no group differences in infections or musculoskeletal disorders, including myalgia (five [3%] patients on simvastatin and nine [6%] on placebo). Rhabdomyolysis and myoglobinuria were not reported and there were no differences in serum creatine phosphokinase.

**INTERPRETATION:**

We found no beneficial effect of simvastatin as add-on therapy to interferon beta-1a. Although unlikely, we can not exclude that combination of other statins with other disease-modifying drugs still could be beneficial.

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