Simvastatin for cognitive deficits and behavioural problems in patients with neurofibromatosis type 1 (NF1-SIMCODA): a randomised, placebo-controlled trial

Thijs van der Vaart, Ellen Plasschaert, André B Rietman, Marleen Renard, Rianne Oostenbrink, Annick Vogels, Marie-Claire Y de Wit, Mie-Jef Descheemaeker, Yvonne Vergouwe, Coriene E Catsman-Berrevoets, Eric Legius, Ype Elgersma, Henriëtte A Moll

Summary

Background Neurofibromatosis type 1 is a common genetic disorder characterised by neurocutaneous manifestations and cognitive and behavioural problems. Statins were shown to reduce analogous learning deficits in a mouse model of the disease, but a short-term trial in humans was inconclusive. We aimed to assess the use of simvastatin for the improvement of cognitive and behavioural deficits in children with neurofibromatosis type 1 for 12 months.

Methods In this randomised, double-masked, placebo-controlled trial, we recruited children with genetically confirmed neurofibromatosis type 1 aged 8–16 years from two national referral centres in the Netherlands and Belgium. Those with symptomatic CNS abnormalities or on neurotropic medication, including stimulants, were excluded. Eligible patients were randomly assigned (1:1) via a computer-generated, permuted-block list to simvastatin (10 mg per day in month 1, 20 mg per day in month 2, and 20–40 mg per day in months 3–12) or placebo for 12 months. Investigators, participants, and parents were masked to treatment assignment. Primary outcome measures were full-scale intelligence (Wechsler intelligence scale for children), attention problems (child behaviour checklist, parent-rated [CBCL]), and internalising behavioural problems (CBCL). We did intention-to-treat analyses (of all patients who had outcome data) using linear regression of the 12 month outcome scores, adjusted for baseline performance. This trial is registered with the Netherlands Trial Register, number NTR2150.

Findings We randomly assigned 84 children to a treatment group (43 to simvastatin, 41 to placebo) between March 9, 2010, and March 6, 2012. We did not assess outcomes in two patients in the placebo group because they needed additional drug therapy. Simvastatin for 12 months had no effect on full-scale intelligence (treatment effect compared to placebo was –0.2 points [-3.3 to 3.1]; p=0.96). 38 (88%) of 43 patients on simvastatin and 39 (95%) of 41 patients on placebo reported adverse events, which were serious in two and four patients, respectively.

Interpretation 12 month simvastatin treatment did not ameliorate cognitive deficits or behavioural problems in children with neurofibromatosis type 1. The use of 20–40 mg simvastatin per day for cognitive enhancement in children with neurofibromatosis type 1 is not recommended.

Funding The Netherlands Organization for Health Research and Development (ZonMw), Research Foundation Flanders (FWO-Vlaanderen), Marguerite-Marie Delacroix Foundation, and the Dutch Neurofibromatosis Association (NFVN).

Introduction Neurofibromatosis type 1 is a common autosomal-dominant disorder, with a prevalence of 1 in every 2500–3000 births.1 It is caused by loss-of-function mutations in the NFI gene, which encodes neurofibromin, a negative regulator of rat-sarcoma viral oncogene homologue (Ras). Neurofibromatosis type 1 is characterised by cutaneous café-au-lait spots, neurofibromas, and cognitive and behavioural problems.2 Up to 80% of children aged 6–18 years with neurofibromatosis type 1 present with moderate to severe impairment in one or more areas of cognitive functioning, and 40% attend special education.3 Moreover, 30–40% of children with neurofibromatosis type 1 fulfil criteria for attention deficit hyperactivity disorder and up to 60% have problems with executive functioning.4 The average intelligence quotient (IQ) is 10–15 points lower in these children than in population or sibling control groups.5,6 Parents of children with neurofibromatosis type 1 frequently report difficulties in their child’s social daily activities and a high rate of internalising behavioural problems, such as anxiety or mood disorders.7,8 Taken together, cognitive and behavioural deficits lead to lower academic achievement and loss of quality of life,9,10 persisting into adulthood.11

The learning and attention deficits noted in patients with neurofibromatosis type 1 are reported in the NFI1” mouse model,12,13 accompanied by a decrease in synaptic plasticity.14,15 These animal studies have shown that the plasticity and behavioural deficits are reversed by reducing Ras activity.16,17 Ras activity requires farnesylation, which allows Ras to anchor to the plasma membrane where it
can be activated by growth-factor receptors and their
adaptor proteins. Since cholesterol is an obligate precursor
of farnesyl, inhibitors of 3-hydroxy-3-methylglutaryl
coenzyme A (HMG-CoA) reductase have been suggested
as a potential therapy for neurofibromatosis type 1. Indeed,
lovastatin normalised Ras activity, rescued synaptic
plasticity deficits, and restored learning and attention deficits in the Nf1+/− mouse model.19 Results of a
small, open-label, single-arm study of lovastatin in
children with neurofibromatosis type 1 suggested that
lovastatin improved memory and attention, and
normalised default network functional connectivity
measured with resting state functional MRI.15,16

However, lovastatin is not approved or marketed in
many parts of the world, including the European Union.
The closest approved alternative, simvastatin, is similar
in structure, pharmacokinetics, and blood–brain barrier
permeability. Moreover, simvastatin is a slightly more
potent inhibitor of HMG-CoA reductase and is better at
reducing HMG-CoA reductase activity in neurons than is
lovastatin.17,18 Although findings of a randomised
controlled trial reporting the short-term effect of
simvastatin in children with neurofibromatosis type 1
showed no effect after 12 weeks on a set of primary
outcome measures,4 a significant improvement was
reported for a secondary outcome measure, the object
assembly subtask of the Dutch translation of the third
edition of the Wechsler intelligence scale for children
(WISC-III-NL).4 Although this trial had an overall
negative outcome, it had some limitations that might have
affected its results: children on stimulant-
medication were not excluded, and 12 week treatment
was short, with only 4 weeks at the highest target dose. A
longer treatment duration would have allowed the
assessment of the effects on global cognitive functioning,
daily life functioning, and behaviour, and might have
been necessary to show clinical benefits.

Given the large amount of safety data in children19 and
worldwide marketing authorisation of simvastatin, we
aimed to improve upon the limitations of this previous
trial by assessing the use of simvastatin for the treatment
of cognitive and behavioural deficits in children with
neurofibromatosis type 1 for 12 months.

Methods

Study design and participants

We undertook this randomised, parallel-group, placebo-
controlled trial in two national referral centres: Erasmus
MC (Rotterdam, Netherlands) and UZ Leuven (Leuven,
Belgium). We screened patients aged 8–16 years with
genetically confirmed neurofibromatosis type 1 for
eligibility. Genetic counselling and testing for neuro-
fibromatosis type 1 is part of routine care and was done
independently of this trial. The rationale for genetic
confirmation was the substantial overlap in phenotypes
between neurofibromatosis type 1 and related disorders
(e.g., Legius syndrome).20 Exclusion criteria were: use of
neurotropic medication, including stimulant, anti-
psychotic, antiepileptic, anti-anxiety, and antidepressant
drugs, or current simvastatin use; symptomatic CNS
abnormalities; insufficient comprehension of the Dutch
language; severely impaired vision or deafness; segmental
neurofibromatosis type 1; or an IQ below 48.

We obtained informed oral and written consent from
parents and assent from children of 12 years and older.
Local and national institutional review boards approved
the protocol. The trial was done in agreement with the
Declaration of Helsinki (version 2008) and Good Clinical
Practice guidelines.

Randomisation and masking

Eligible patients were randomly assigned (1:1) by the
local hospital pharmacist to simvastatin or matched
placebo according to computer-generated, permuted
block randomisation lists (ten participants per block,
stratified by centre) that were provided by the Department
of Biostatistics, Erasmus MC, with medication numbers
in the order of enrolment. All investigators, participants,
and their parents were masked to treatment allocation.
We achieved blinding by using capsules of identical
colour, shape, size, weight, smell, and taste.

Procedures

Participants took 10 mg per day of simvastatin or matched
placebo once daily in the morning during the first month
and 20 mg per day once daily in the morning during the
second month. During months 3–12, dosing was fixed at
20 mg per day for children aged 12 years and younger
and 40 mg per day for adolescents older than 12 years.

We assessed efficacy outcome measures at baseline and
at the end of month 12 of treatment. Since no standard
measure exists to assess improvement of cognition in
patients with neurofibromatosis type 1, we included a
broad range of validated tests and questionnaires that are
sensitive to the cognitive and behavioural deficits in this
group of patients. Outcome measures included constructs
that were similar to those that improved in mouse models
receiving statins:21 visual-spatial memory and attention;
improvements in daily life behavioural problems rated by
parents; and global cognitive functioning.

We used three primary outcome measures that are
relevant to daily life functioning and academic achieve-
ment: full-scale intelligence (WISC-III-NL),22 parent-
reported attention problems (child behaviour checklist
[CBCL]23), and parent-reported internalising behavioural
problems (CBCL). The attention problems scale of the
CBCL consists of items screening for problems in
directing and sustaining attention, controlling
impulsivity, and hyperactivity. Secondary outcomes were
visual-spatial memory (Rey complex figure test–delayed
recall),24 attention (Stroop colour–word interference test),25
teacher-reported school performance (teacher report
form),26 parent-reported psychosocial quality of life (child
health questionnaire–parent form 50 [CHQ-PF50]),27

For the study protocol see
http://www.erasmusmc.nl/nf1-
simcoda
343 patients assessed for eligibility

122 excluded
64 ADHD medication
21 CNS abnormalities
17 other medication
9 language problems
7 no mutation found
2 vision problem
2 segmental neurofibromatosis 1

221 eligible

116 declined
56 too much of an investment in time and effort
21 cognitive function not perceived as problem
10 other reasons
29 no reason specified
21 no response

84 randomly assigned

41 allocated and received placebo
43 allocated and received simvastatin

2 lost to follow-up
2 behavioural problems requiring drug therapy

2 non-compliant

0 lost to follow-up

39 analysed
43 analysed

Figure 1: Trial profile
ADHD=attention deficit hyperactivity disorder.

See Online appendix

patient-reported internalising behavioural problems (youth self-report [YSR] form, completed by patients aged ≥11 years).21 and fine motor coordination (grooved pegboard test).22 All neuropsychological tests were developed for children and were written or presented in Dutch. For most outcome measures, we used age-standardised scores. The mean average IQ for the general population is 100 (SD 15), with higher IQ WISC-III-NL test scores indicating higher intelligence. For CBCL and YSR, data were represented as T scores, with a mean average of 50 and an SD of 10 in the general population, with higher scores indicative of more problems. The Rey complex figure test (for which a higher score suggests a better visual-spatial memory) and CHQ-PF50 (for which a higher score suggests a better quality of life) are presented using Z scores, with 0 representing the mean for the normal sample with an SD of 1. Teacher-reported school performance was calculated on a scale from 2 to 10, by summation of 5-point scores on topics of language and arithmetic, in which higher scores were given for greater ability in each area. For teacher-reported school performance, Stroop colour–word test (for which a lower score suggests better attention), and grooved pegboard test (for which a lower score suggests better fine motor coordination), raw scores were used, since no appropriate normal groups are available for the entire age range. Measurements taken before and after administration of study drug were done by the same neuropsychologist (either ABR or EP).

Adverse events and study compliance were monitored by monthly telephone contact and by visits to the outpatient clinic at baseline and at 1, 3, 6, 9, and 12 months. Adverse events were classified according to WHO adverse reaction terminology and graded according to the National Cancer Institute common terminology criteria for adverse events. Blood was drawn at baseline and at 1, 6, 9, and 12 months to measure: alanine aminotransferase, aspartate aminotransferase, and creatine phosphokinase to screen for laboratory adverse events; and total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides to assess lower limits of lipid concentrations and to monitor compliance. Further details on procedures are presented in the appendix.

Statistical analysis
We used data from the intention-to-treat population—which consisted of all participants with outcome data—for all primary and secondary analyses, without imputation of missing values. Data from all patients were used for safety analyses—even those without efficacy outcome data. We analysed primary and secondary outcome measures using linear regression for the effect of treatment group on the score at 12 months, adjusted for baseline performance in the bivariable analysis and adjusted for baseline performance, age, and sex in the multivariable analysis. The cutoff level for significance was set at p<0·05, ignoring multiple testing. We analysed lipid blood concentrations using the generalised linear mixed model procedure with the interaction of time and treatment as the variable of interest. Sample size calculation suggested that inclusion of 84 participants (85% power; α=0·05) would be sufficient to detect a clinically relevant treatment effect of 7·5 full-scale intelligence points (0·5 SD), adjusted for baseline performance, and an increase or decrease of 5 T-score points (SD 0·5) for attention problems and internalising behavioural problems. Inclusion of 84 participants would lead to greater than 80% power on the coprimary outcome measures of attention problems and internalising behavioural problems. Because of low inclusion rates, the protocol was amended from 90% power and 106 participants to 85% power and 84 participants in the second recruitment year, without outcome knowledge and with approval from review boards. We planned the analysis before unmasking according to the study protocol. All data were analysed using IBM SPSS Statistics for Windows (version 20.0).
Role of the funding sources
The sponsors of the study had no role in the conception and design of the trial, the collection, analysis, and interpretation of the data, the writing of the manuscript, or the decision to publish the results. All authors had full access to all of the data in the study, and EL, YE, and HAM had final responsibility for the decision to submit for publication.

Results
We screened 343 patients for eligibility, of whom 221 were eligible. Between March 9, 2010, and March 6, 2012, we obtained informed consent from 84 patients or their parents. They were randomly assigned to 12 months of treatment with simvastatin (n=43) or placebo (n=41). Two patients in the placebo group were lost to follow-up before outcome could be assessed because they had behavioural problems that required drug therapy. Two participants in the placebo group discontinued study medication, but were available for outcome assessment (figure 1). Median compliance per patient was 96% (IQR 93–100), measured by counting returned capsules. Baseline demographic and disease characteristics were generally balanced between both treatment groups, although more patients in the simvastatin group were male than in the placebo group (table 1). At baseline, average full-scale intelligence was 83·3 points (SD 15·6) and 46 (55%) participants had attention problems scored on the CBCL of more than 1 SD above the mean of the general population. Median age was 11·5 years (range 7–9–16·0).

12 months of simvastatin had no significant effect on full-scale intelligence (treatment effect –1·3 IQ points [95% CI –3·8 to 1·3]; p=0·33), attention problems (–1·6 T-score points [–4·3 to 1·0]; p=0·23), or internalising behavioural problems (–0·1 [–3·3 to 3·1]; p=0·96) when adjusted for baseline performance (table 2). Additional adjustment for age and sex produced similar results (table 2). Simvastatin had no significant effects on any of the secondary outcome measures, including visual-spatial memory and attention (table 2). Additional adjustment for age and sex produced similar results (table 2). Simvastatin had no significant effect on any of the secondary outcome measures, including visual-spatial memory and attention (table 2).

After 1 month (10 mg simvastatin per day), mean total cholesterol in the simvastatin group had decreased by 0·78 mmol/L (95% CI 0·54–1·03) more than it had in the placebo group and LDL cholesterol decreased by 0·79 mmol/L (0·56–1·01). Cholesterol concentrations had decreased no further at 6, 9, or 12 months. HDL cholesterol and triglycerides remained stable over the course of the study (appendix).

Most adverse events were mild or moderate and frequency was similar between groups (table 3). 38 (88%) of 43 patients in the simvastatin group and 39 (95%) of 41 patients in the placebo group reported at least one adverse event. No increased incidence of myalgia, myopathy, or rhabdomyolysis was reported in patients given simvastatin compared with patients given placebo (appendix). Serious adverse events occurred in six patients: two in the simvastatin group and four in the placebo group. These events included continuing growth of plexiform neurofibromas (in two patients receiving simvastatin and one patient receiving placebo) and progressive scoliosis (two patients receiving placebo), all requiring surgery, and hospital admission for gastritis (one patient receiving placebo).

Results of laboratory screens showed a few mild and transient increases in liver enzymes and creatine kinase in both groups (table 3); none led to cessation of therapy.
treatment. No participants reached the predefined lower limits for total cholesterol, HDL-cholesterol, or triglycerides (non-fasting). In the simvastatin group, seven children had one (n=3) or more (n=4) LDL-cholesterol measurements below the predefined lower threshold, but no action was recommended by the data and safety monitoring board, since other values were within the normal range. Nine (53%) of 17 girls receiving simvastatin advanced one or more Tanner stages of puberty during the trial, compared with 16 (67%) of 24 receiving placebo. 14 (54%) of 26 boys receiving simvastatin and seven (54%) of 13 receiving placebo advanced one or more Tanner stages. Two girls in the placebo group were not included in this analysis because they did not undergo postbaseline Tanner stage assessments.

**Discussion**

Here we present the outcome of our randomised, double-masked, placebo-controlled trial aimed at improving cognitive deficits in children with neurofibromatosis type 1. Our results showed that simvastatin treatment for 12 months had no effect on full-scale intelligence, attention problems, or internalising behavioural problems. Moreover, we found no indications of efficacy on a carefully selected range of predefined secondary

### Table 2: Primary and secondary outcome measures at baseline and 12-month follow-up

<table>
<thead>
<tr>
<th>Primary outcome measures</th>
<th>Simvastatin</th>
<th>Placebo</th>
<th>Adjusted for baseline score</th>
<th>Adjusted for baseline score, age, and sex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full-scale intelligence (WISC-III-NL)*</td>
<td>n=43</td>
<td>n=39</td>
<td>-1·3 (-3·8 to 1·3)</td>
<td>0·33</td>
</tr>
<tr>
<td>Baseline IQ</td>
<td>83·8 (16·1)</td>
<td>82·3 (15·5)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>12 month IQ</td>
<td>85·7 (16·0)</td>
<td>85·4 (16·4)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Attention problems (CBCL)†</td>
<td>n=42‡</td>
<td>n=39</td>
<td>-1·6 (-4·3 to 1·0)</td>
<td>0·23</td>
</tr>
<tr>
<td>Baseline score</td>
<td>61·1 (9·0)</td>
<td>62·0 (7·6)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>12 month score</td>
<td>58·8 (7·4)</td>
<td>60·9 (9·0)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Internalising behavioural problems (CBCL)†</td>
<td>n=42‡</td>
<td>n=39</td>
<td>-0·1 (-3·3 to 3·1)</td>
<td>0·96</td>
</tr>
<tr>
<td>Baseline score</td>
<td>54·9 (10·6)</td>
<td>56·1 (10·0)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>12 month score</td>
<td>54·0 (10·0)</td>
<td>54·5 (10·0)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary outcome measures</th>
<th>Simvastatin</th>
<th>Placebo</th>
<th>Adjusted for baseline score</th>
<th>Adjusted for baseline score, age, and sex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual-spatial memory (Rey complex figure test-delayed recall)*</td>
<td>n=42§</td>
<td>n=39</td>
<td>-0·2 (-0·6 to 0·2)</td>
<td>0·34</td>
</tr>
<tr>
<td>Baseline Z score</td>
<td>-2·0 (0·9)</td>
<td>-2·0 (1·1)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>12 month Z score</td>
<td>-1·9 (1·0)</td>
<td>-1·7 (1·2)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Attention (Stroop colour–word test)†</td>
<td>n=41¶</td>
<td>n=37¶</td>
<td>7·5 (-3·3 to 16·2)</td>
<td>0·14</td>
</tr>
<tr>
<td>Baseline raw score</td>
<td>72 (39)</td>
<td>64 (45)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>12 month raw score</td>
<td>59 (31)</td>
<td>47 (27)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Teacher-rated school performance*</td>
<td>n=34</td>
<td></td>
<td></td>
<td>n=30</td>
</tr>
<tr>
<td>Baseline raw score</td>
<td>5·8 (2·2)</td>
<td>5·7 (2·4)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>12 month raw score</td>
<td>6·2 (1·9)</td>
<td>6·0 (1·9)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Psychosocial quality of life (CHQ-PF50)*</td>
<td>n=40**</td>
<td>n=38**</td>
<td>0·02 (-0·22 to 0·25)</td>
<td>0·89</td>
</tr>
<tr>
<td>Baseline Z score</td>
<td>-0·06 (0·80)</td>
<td>-0·07 (0·74)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>12 month Z score</td>
<td>0·15 (0·60)</td>
<td>0·13 (0·80)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Internalising behavioural problems (youth self-report)†</td>
<td>n=23†</td>
<td>n=24†</td>
<td>-1·7 (-6·5 to 3·1)</td>
<td>0·48</td>
</tr>
<tr>
<td>Baseline T score</td>
<td>56·4 (11·9)</td>
<td>53·0 (8·3)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>12 month T score</td>
<td>51·9 (9·9)</td>
<td>51·7 (9·8)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fine motor coordination (grooved pegboard test, dominant hand)†</td>
<td>n=43</td>
<td>n=39</td>
<td>-3·8 (-8·8 to 1·3)</td>
<td>0·14</td>
</tr>
<tr>
<td>Baseline raw score</td>
<td>94 (29)</td>
<td>84 (23)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>12 month raw score</td>
<td>80 (18)</td>
<td>79 (18)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

- Data are mean (SD), unless otherwise specified. WISC-III-NL=Wechsler intelligence scale for children, third edition, Dutch translation. CBCL=parent-reported child behaviour checklist. CHQ-PF50=child health questionnaire–parent form 50. *Higher is better. †Lower is better. **Data missing for one patient in the simvastatin group because the questionnaire was not returned by the parents. ††Data missing for one patient in the simvastatin group because they were omitted from the test battery erroneously. ‡‡Data missing for two patients in each group because they were unable to take the test because of reading disability. ‧Data missing for nine patients in each group because arithmetic and language topics were classified by teachers as not applicable to these patients. §§Data missing for one patient in the simvastatin group because the questionnaire was not returned, and for two patients in the simvastatin group and one in the placebo group because essential items were not completed on the checklist. ††Children younger than 11 years were deemed too young to be given the youth self-report form (20 patients in the simvastatin group; 15 patients in the placebo group).
outcome measures. Hence, this trial refutes a role for simvastatin in treatment of cognitive or behavioural problems in children with neurofibromatosis type 1.

Unfortunately, despite the many promising drugs that have been identified in mouse models of cognitive disorders, translational studies with placebo-controlled trial designs are rare for cognitive disorders caused by single-gene mutations. This situation is also true for neurofibromatosis type 1 (panel). The absence of good clinical studies encourages off-label prescription, which is a major concern, particularly when the drug is readily available to the patient.

In this study, the cognitive and behavioural profile of the study population at baseline (table 1) was fairly representative of the cognitive profile in the general neurofibromatosis type 1 population.13−15 Sample size was adequate, because we could confidently rule out a positive change of more than 1·3 points in full-scale intelligence, a reduction of attention problems of more than 4·3 T-score points, and a reduction of internalising behavioural problems of more than 3·3 T-score points (table 2). Furthermore, we achieved a low attrition rate and high medication compliance, which suggests that medium-term to long-term trials for cognitive dysfunction are feasible in this population.

The dosing was based on the maximum recommended daily dose for treatment of children with familial hypercholesterolaemia.16 At least in the liver, maximal inhibition of the HMG-CoA reductase pathway was achieved in patients on simvastatin, shown by the substantial reduction of blood cholesterol concentrations after 1 month (appendix). Whether similar inhibition of the HMG-CoA reductase pathway was achieved in the brain is unknown. It is possible that higher doses are necessary to achieve biological effects in human beings. However, increasing the dose would increase safety concerns, including the risk of myopathy, which was a major concern, particularly when the drug is readily available to the patient.

We assumed 12 months of treatment was long enough to show a discernible effect on full-scale intelligence or other neuropsychological tests is unknown. In view of the broad range of tests and validated questionnaires in this study, selection of different outcome measures would have been unlikely to change the conclusions on the effect of simvastatin treatment.

Our study population was selective in two ways. First, it excluded children who had been taking stimulant medication or in healthy children taking music lessons.25 However, how much time a human brain would need to show a discernible effect on full-scale intelligence or other neuropsychological tests is unknown. In view of the broad range of tests and validated questionnaires in this study, selection of different outcome measures would have been unlikely to change the conclusions on the effect of simvastatin treatment. Second, of 343 children who were screened, 64 (19%) were excluded from the trial because they had been taking...
Articles

Panel: Research in context

Systematic review
We did a systematic search of PubMed on July 8, 2013, for additional cognitive trials in neurofibromatosis type 1. Search terms included “neurofibromatosis”, “cognition”, “attention”, “behaviour”, and “clinical trial”. Of 25 articles found, four described three clinical trials in patients with neurofibromatosis type 1. A 12 week randomised placebo-controlled trial in 61 children with neurofibromatosis type 1 showed no effect of simvastatin on cognitive function and MRI abnormalities, with the notable exception of the significant effect on one secondary outcome measure: the object assembly subtask of the Wechsler intelligence scale for children. Furthermore, results of a phase 1 single-arm open-label study of lovastatin in 23 children with neurofibromatosis type 1 suggested lovastatin improved memory and attention, accompanied by normalisation of default network functional connectivity measured with resting-state functional MRI in a subset of the participants.

These seemingly encouraging results might be attributable to normal cognitive development, test–retest improvements, or placebo effects. A third study was a single-arm 1 year study of methylphenidate to treat attention problems in children with neurofibromatosis type 1 and comorbid attention deficit hyperactivity disorder, and results showed a decrease in attention problems in children who received the drug.

Interpretation

In this 12 month trial, use of simvastatin provided no benefit over placebo on full-scale intelligence, behavioural problems, visual-spatial memory, attention, motor coordination, school performance, and quality of life. These findings are in contrast with results from the previous single-arm study, but largely consistent with the smaller randomised controlled trial that measured short-term effects of simvastatin on neuropsychological test scores and MRI abnormalities. We conclude that the number of trials is limited, and more studies are needed to identify effective treatments for cognitive and behavioural problems in children with neurofibromatosis type 1.

stimulant medication. Despite this selection, 46 (55%) participants had attention problems of more than 1 SD above population norms, suggesting that attention problems were prevalent in the study population.

Children were eligible for this study irrespective of their baseline neuropsychological test scores, since several difficulties are associated with selecting participants according to baseline performance. First and most important, the subgroup of children with neurofibromatosis type 1 that might benefit most from drug treatment is unknown. Also, any upper or lower limit of functioning would be arbitrary. Therefore, we chose to recruit children irrespective of baseline deficits and to do subgroup analyses if any benefits were noted in primary analysis.

Differences between lovastatin and simvastatin are unlikely to explain our negative results, since the rationale for using statins in neurofibromatosis type 1 is their ability to reduce Ras farnesylation, for which mevalonate is an obligate precursor in the synthesis of both farnesyl moieties and cholesterol. However, we cannot completely exclude off-target effects that are exclusive to lovastatin. A phase 2 randomised trial of lovastatin for 16 weeks is underway to assess its effects on visual spatial learning and sustained attention in children with neurofibromatosis type 1.

The preclinical studies on which this study was predicated were done exclusively in a mouse model of neurofibromatosis type 1, for which underlying human pathophysiological changes might not be sufficiently analogous. For instance, we cannot exclude that certain pathological changes frequently reported in patients with neurofibromatosis type 1, such as microstructural changes of white brain matter identified with diffusion tensor imaging or changes in corpus callosum thickness, contribute to cognitive deficits and might not be responsive to statins. However, important similarities in neurophysiology are reported between patients with neurofibromatosis type 1 and the Nf1−− mouse model. For example, neurofibromatosis type 1 seems to affect working memory and attention in both human beings and rodents through cortical inhibition of corticostriatal pathways. Additionally, behavioural deficits in patients with neurofibromatosis type 1 and mice are very similar: most notably in their analogous deficits in (virtual) water maze performance. Mechanically, GABAergic dysfunction has been observed in both the mouse model and patients.

Nevertheless, in view of the results of our trial, further insight into the pathophysiology of neurofibromatosis type 1 will be necessary to explore other targetable disease mechanisms.

Contributors

TvdV contributed to study design, grant writing, study planning, data collection, data analysis, data interpretation, writing of the first draft of the report, and report revision. EP contributed to study planning, data collection, neuropsychological testing, data analysis, data interpretation, writing of the report, and report revision. ABR contributed to study design, data collection, neuropsychological testing, data analysis, data interpretation, writing of the report, and report revision. MR contributed to data collection and clinical follow-up. RO contributed to study design, grant writing, data collection, clinical follow-up, data interpretation, and report revision. M-JD contributed to data interpretation and report revision. YY contributed to data analysis, data interpretation, and report revision. CEC-B contributed to study design, grant writing, clinical follow-up, data interpretation, and report revision. EJ is a co-principal investigator and contributed to grant writing, study planning, data interpretation, and report revision. YE is a co-principal investigator and contributed to conception of the study, study design, grant writing, study planning, data interpretation, and report revision. HAM is a co-principal investigator and contributed to conception of the study, study design, grant writing, study planning, patient follow-up, data interpretation, and report revision.

Conflicts of interest

All authors declare that they have no conflicts of interest.
Acknowledgments
We thank all children and families for participating in this trial. We thank B Manai, A de Goede-Bolder, C P Bowman, R Zaal, and S Vandenput for assistance during study conduct and E W Steyerberg, J B C de Klerk, Y B de Rijke, L C Krab, and S A Kushner for valuable discussions. We also thank clinicians throughout the Netherlands and Belgium for referring patients, and the Dutch and Flemish patient organisations (Neurofibromatose Vereniging Nederland, NF-Kontakt) for their ongoing support.

References
21. Verhulst FC, Van der Ende J, Koot HM. Handleiding voor de CBCL/4–18. Rotterdam: Academic Medical Center Rotterdam/ Erasmus University, Sophia Children’s Hospital, Department of Child and Adolescent Psychiatry, 1996.