# CLINICAL PHARMACOLOGY GRAND ROUNDS

# Simvastatin treatment for inflammatory attacks of the hyperimmunoglobulinemia D and periodic fever syndrome

**Hyperimmunoglobulinemia D (hyper-IgD) and periodic fever syndrome, a hereditary autoinflammatory syndrome, is characterized by lifelong recurrent episodes of fever and inflammation. No effective treatment is known. It is caused by a defect of mevalonate kinase, an enzyme that follows 3'-hydroxy-3'-methylglutaryl–coenzyme A (HMG-CoA) reductase in the isoprenoid pathway. We wanted to test the hypothesis that inhibition of HMG-CoA reductase would ameliorate the inflammatory attacks. Six patients with hyper-IgD syndrome and proven mevalonate kinase deficiency were followed up for 2 treatment periods with either simvastatin, 80 mg/d, or placebo for 24 weeks, separated by a 4-week washout period in a double-blind fashion. Simvastatin resulted in a drop in urinary mevalonic acid concentration in all patients and decreased the number of febrile days in 5 of 6 patients. No side effects were observed. These data offer preliminary evidence for the hypothesis that simvastatin may improve inflammatory attacks in the hyper-IgD syndrome. This highlights the anti-inflammatory properties of HMG-CoA reductase inhibition. (Clin Pharmacol Ther 2004;75:476-83.)**

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Hyperimmunoglobulinemia D (hyper-IgD) and periodic fever syndrome (HIDS; Mendelian Inheritance in Men [MIM] No. 260920) is a rare hereditary autoinflammatory syndrome caused by mutations in the mevalonate kinase gene.[1,2] Patients with HIDS have periodic fever episodes that usually start from the first year of life and are characterized by high fever, lymphadenopathy, abdominal distress, myalgias, and skin lesions.[3] These inflammatory episodes generally last for 4 to 6 days and recur every 4 to 6 weeks.

Mevalonate kinase is one of the central enzymes in isoprenoid metabolism, which has numerous end products such as cholesterol, ubiquinone, and dolichol and is also essential for isoprenylation of proteins (Fig 1). Me-

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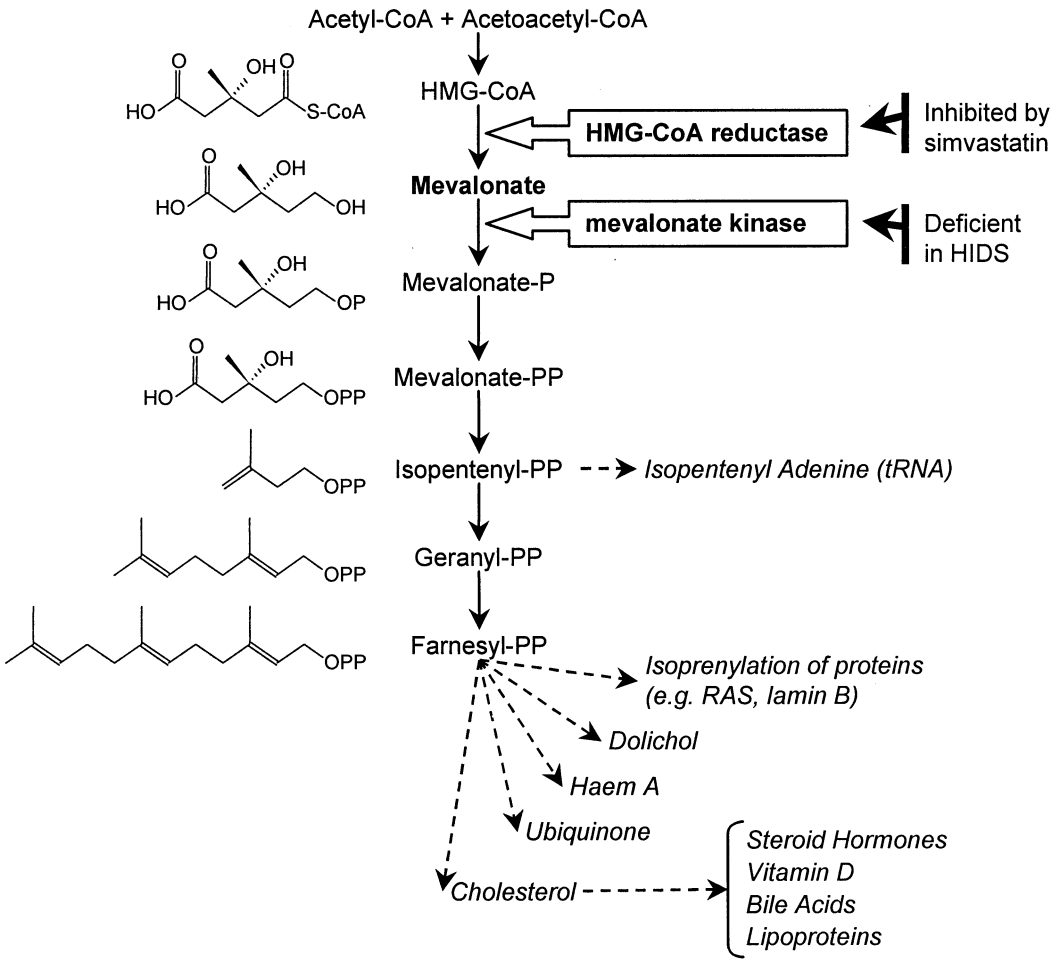


**Fig 1.** Schematic representation of isoprenoid metabolism with its end products. Indicated is the metabolic defect in hyperimmunoglobulinemia D and periodic fever syndrome (HIDS) and the point of inhibition by simvastatin. HMG-CoA, 3'-Hydroxy-3'-methylglutaryl–coenzyme A; tRNA, transfer RNA; P, phosphate; PP, pyrophosphate

valonic acid, or mevalonate, is the product of the enzyme 3'-hydroxy-3'-methylglutaryl–coenzyme A (HMG-CoA) reductase.[4] The mutations in the mevalonate kinase gene lead to deficient mevalonate kinase enzyme activity and accumulation of its substrate, mevalonic acid, most notably during fever attacks. However, it is not exactly clear how this results in the inflammatory phenotype of HIDS.

Treatment options available for HIDS do not reflect our current understanding of the pathophysiologic characteristics of the disease. Thus far, therapeutic experiments have sought to curtail the inflammatory response in HIDS and have met with mixed results. For example, thalidomide (200 mg), given as an inhibitor of tumor necrosis factor response, failed to elicit a beneficial effect in a controlled clinical trial.[5] Uncontrolled evidence suggests that a small proportion of patients benefit from prednisolone, and recently, open-labeled use of etanercept reduced the frequency and severity of symptoms in patients with HIDS.[6] Although etanercept has shown a beneficial effect, potential side effects such as the increased risk of infections and severe neurologic damage[7,8] may preclude its prolonged use. Moreover, it is not known whether the beneficial initial response is followed by sustained improvement over a longer period of time. However, in our opinion noncontrolled clinical observations are not the most optimal setting in HIDS, because of the highly variable nature of the frequency and severity of the fever attacks. This calls for a more rigorous approach.

**Table I.** Patient characteristics

| *Patient No.* | *Mutations in mevalonate kinase* | *Mevalonate kinase enzyme activity (%)* | *Maximal serum IgD (U/mL)* |
|---|---|---|---|
| 1 | V377I/H20P | 8.5 | 450 |
| 2 | V377I/I268T | 7.2 | 900 |
| 3 | V377I/H20P | 11.3 | 4224 |
| 4 | V377I/del92bp | 10.5 | 809 |
| 5 | V377I/V377I | 5.7 | 376 |
| 6 | V377I/H20P | ND | 1140 |

IgD, Immunoglobulin D; ND, not done.

The discovery of mevalonate kinase as the gene implicated in HIDS led us to hypothesize that patients with HIDS might benefit from the use of an HMG-CoA reductase inhibitor such as simvastatin. In theory, this would restore the balance in the isoprenoid metabolism and reduce the mevalonic acid overload. Despite these theoretic considerations, preliminary data from a single study in 2 children with classical mevalonic aciduria, the severe form of mevalonate kinase deficiency, are not encouraging.[9] Short-term treatment with low-dose lovastatin (5 mg initially and 10 mg later) precipitated a severe crisis in both, prompting discontinuation of the statin. Therefore we first explored whether statins could be tolerated by HIDS patients (who have a mild mevalonate kinase deficiency). In a 4-week pilot study with high-dose atorvastatin (80 mg/d) in 3 HIDS patients, we observed no precipitation of inflammatory attacks and, more importantly, no side effects. These results encouraged us to investigate our hypothesis in a randomized, double-blind crossover study of 6 HIDS patients.

## METHODS

We selected patients from the Nijmegen HIDS registry[10] when they fulfilled the following entry criteria for the study: (1) mevalonate kinase gene mutations on both alleles, (2) age more than 16 years, and (3) frequent attacks (>1 per 6 weeks). The study was approved by the local medical ethical committee, and all participants gave written informed consent.

The follow-up period of 52 weeks consisted of 2 treatment periods of 24 weeks, with a 4-week washout period between them. Patients were randomized to receive simvastatin, 80 mg/d, during the first or second treatment period, with placebo tablets during the other period. A clinical pharmacist not directly involved in the study prepared a simple computer-generated random-number list for randomization. The code was held at the Department of Clinical Pharmacy, University Medical Center St Radboud, Nijmegen, The Netherlands, and was only opened after all data had been entered into a computer for analysis. Concomitant medications were allowed throughout the study and recorded.

The primary outcome measure was defined as the number of febrile days. Secondary outcome parameters were number of fever attacks, urinary concentration of mevalonic acid, and serum lipid concentrations. Attacks were defined as fever (>38.5°C) together with one or more of the following symptoms: abdominal distress (pain, vomiting, or diarrhea), joint involvement (arthralgia, arthritis), skin lesions, or lymphadenopathy. Patients used weekly diary cards to register the number, duration, and severity of attacks on a visual analog scale and to record possible side effects of study medication. At each clinic visit (week 0, 12, 24, 28, 40, and 52), blood was drawn to determine concentrations of plasma ALT and creatine kinase and serum lipids via an automated enzymatic assay. Patients collected weekly urine samples from which mevalonic acid concentrations were measured by isotope-dilution gas chromatography–mass spectrometry as described previously[11] with slight modification.

GraphPad Prism (version 4.00 for Windows; GraphPad Software, San Diego, Calif) was used for statistical analysis of data. Where appropriate, we used the 2-tailed paired *t* test or 2-tailed Mann-Whitney test. Data are given as mean ± SD, unless stated otherwise. A $P$ value $< .05$ was considered as the threshold for statistical significance.

## RESULTS

***Patients.*** At the start of the study, the Nijmegen HIDS registry contained data on 58 HIDS patients with proven mevalonate kinase deficiency. Patients were excluded because of age (<16 years) (n = 25), infrequent attacks (n = 8), refusal to participate (n = 12), or miscellaneous reasons (lost to clinical follow-up, residence abroad, or homelessness at the start of the study) (n = 7). Four patients (2 men and 2 women) were enrolled in December 2000, and 2 other male patients started in March and September 2001; the patients' mean age was 34 years (range, 17-56 years). Patient characteristics are summarized in Table I. Three patients were randomly assigned to start with placebo in the first 6-month period and then to take simvastatin in the last 6 months; the other 3 patients were treated in the reverse order. All 6 patients completed the follow-up.

Medication used concomitantly with the study medication consisted primarily of acetaminophen, in equal

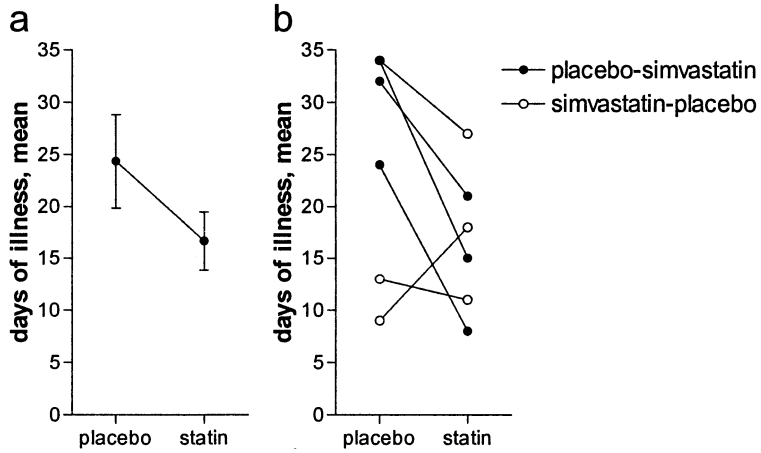


**Fig 2.** Primary outcome measure: number of days of illness in each 6-month period. **a**, Mean number of days of illness and SEM for the total group of patients during placebo and simvastatin. **b**, Individual results for the 6 patients. Indicated are the 2 groups, starting either with placebo (*solid symbols*) or with simvastatin (*open symbols*). This seems to demonstrate an interaction between treatment order and treatment effect; patients who started with placebo had a larger reduction in days of illness during simvastatin.

amounts in the 2 periods. Patient 1 was taking a continuous dose of colchicine, 1.5 mg, throughout the year of follow-up. Patient 6 had been taking oral prednisolone for the year before the study because of severe joint involvement; within 6 weeks of the start of the simvastatin treatment period (the first period in this case), prednisolone had been tapered and stopped without complications.

***Clinical outcome.*** In the complete study period of 52 weeks, the patients registered a total of 44 fever attacks (on average, 1 every 7 weeks per patient) and 262 days of illness (Table II). During the placebo period, a total of 146 febrile days was reported versus 100 days in the simvastatin treatment period; this amounts to a mean of 24.3 ± 11.0 days per patient per 6 months versus 16.7 ± 6.9 days per patient per 6 months (decrease of 7.6 days, or 31%; $P = .12$; 95% confidence interval, −3 to 18.36) (Fig 2). The effect seemed to be more pronounced in the patients who took simvastatin in the second period than in those who started with simvastatin. This might indicate a carryover effect, but the small number of patients precludes a definitive conclusion.

The number of fever attacks was low (total of 23 versus 18 for placebo versus simvastatin) (Table II). For the whole group, a mean number of 3.8 ± 1.2 was observed in the placebo period versus 3.0 ± 1.3 in the simvastatin period. No consistent effect of drug treatment was observed on either severity or duration of attacks (Table II). Four patients had a subjective preference for simvastatin; 1 patient considered the periods equal, and 1 patient preferred the placebo period, although classifying the past year as a "light one" (both of these were in the group taking simvastatin and then placebo) (Table II).

***Lipid spectrum.*** At baseline, the HIDS patients had normal to low-normal serum concentrations of low-density lipoprotein cholesterol (mean, 2.6 ± 1.0 mmol/L). As expected, simvastatin significantly reduced concentrations of serum total cholesterol (mean, 4.8 ± 1.2 mmol/L versus 3.0 ± 0.5 mmol/L at end of treatment; 38% reduction; $P = .016$) and low-density lipoprotein cholesterol (mean, 3.3 ± 0.9 mmol/L versus 1.5 ± 0.7 mmol/L at end of treatment; 55% reduction; $P = .0052$) (Fig 3), with no difference between the 2 treatment-order groups (data not shown).

***Urinary mevalonic acid.*** The 6 patients collected 133 urine samples in the placebo period and 135 samples in the simvastatin period (20 samples were missing). The mevalonic acid concentration mirrored the clinical symptoms, with high peaks up to 14.6 mg/g creatinine during a fever attack (normal value, 0.4 ± 0.18 mg/g creatinine), although discrepancies between mevalonic acid concentration and clinical symptoms can be observed (Fig 4). The mevalonic acid concentration in the placebo period was significantly higher than in the simvastatin treatment period, whether the analysis consisted of median absolute concentrations

**Table II.** Overview of results

| *Patient No.* | *Start** | *Order* | *Subjective preference* | *Febrile attacks, (length and severity score)†* | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | *First period* | | | | |
| 1 | Dec | Simvastatin-placebo | Equal | 4 d, VAS 2 | 4 d, VAS 5 | 3 d, VAS 1 | | |
| 2 | Sept | Simvastatin-placebo | Placebo | 4 d, VAS 7 | 5 d, VAS 9 | 4 d, VAS 6 | 5 d, VAS 4 | |
| 3 | Dec | Placebo-simvastatin | Simvastatin | 7 d, VAS 8 | 8 d, VAS 8 | 9 d, VAS 9 | 8 d, VAS 10 | |
| 4 | March | Placebo-simvastatin | Simvastatin | 12 d, VAS 6 | 6 d, VAS 4 | 6 d, VAS 7 | | |
| 5 | Dec | Placebo-simvastatin | Simvastatin | 8 d, VAS 4 | 7 d, VAS 9 | 7 d, VAS 3 | 8 d, VAS 9 | 4 d, VAS 1 |
| 6 | Dec | Simvastatin-placebo | Simvastatin | 4 d, VAS 1 | 4 d, VAS 3 | 5 d, VAS 1 | 4 d, VAS 1 | 10 d, VAS 1 |

*Month of start in study protocol.
†Individual fever episodes per patient; indicated are duration (in days) and severity as measured by the patient on a visual analog scale (VAS) from 0 to 10 points, with 10 indicating most severe.

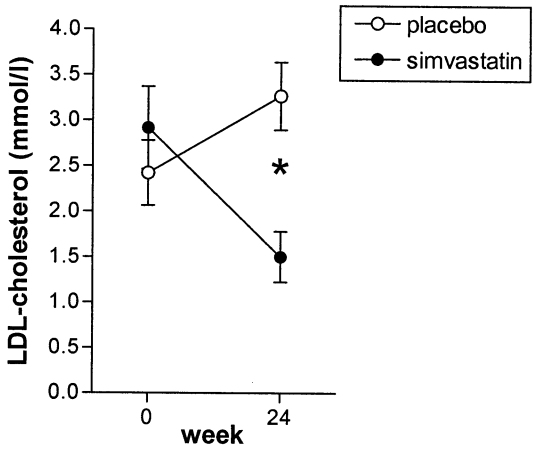


**Fig 3.** Mean serum low-density lipoprotein (LDL) cholesterol concentration of 6 patients at beginning and end of treatment period. *1 Asterisk, $P < .0052$.*

(4.9 mg/g creatinine versus 1.9 mg/g creatinine, 61% reduction; $P < .001$) (Fig 5) or median area under the curve (115.5 mg/g creatinine · wk versus 59.9 mg/g creatinine · wk, $P = .004$). This pattern was consistent for all 6 patients.

***Side effects.*** Side effects were not reported by 5 of 6 patients. Patient 1, who continued receiving a steady dose of 1.5 mg colchicine throughout the study period, reported symptoms of flatulence during the entire year, as well as nightmares with simvastatin and increased tiredness and myalgias while taking placebo. Neither treatment affected creatine kinase or ALT concentrations.

## DISCUSSION

This study is the first to investigate a pharmacologic intervention specifically designed to target the metabolic defect in HIDS. The cohort of patients included in this study is small, which is largely related to the rarity of the disorder (6 patients represented almost 10% of the worldwide known patient population at the start of the study). We observed a positive clinical effect in 5 of 6 patients, with a decrease in the number of febrile days, although the difference did not reach statistical significance.

HIDS has been linked to mutations in the mevalonate kinase gene and decreased mevalonate kinase enzyme activity since 1999,[1,2] but despite intensive research efforts, the actual pathogenesis has yet to be determined. It has been suggested that the primary defect lies in the decreased flux through the isoprenoid metabolism leading to shortage of end products, which is compensated by increased mevalonic acid.[12,13] Alternatively, a high mevalonic acid concentration may in itself be toxic and result in the inflammatory attacks. Mayatepek et al[14] reported a close correlation between the concentration of the proinflammatory mediator leukotriene E4 with the urinary level of mevalonic acid. Although the suggested beneficial effect observed in the current study would not refute the former hypothesis, the results are more in line with the latter hypothesis, even more so because clinical improvement is mirrored by lower mevalonic acid excretion. However, it is possible that inhibition of HMG-CoA reductase results in a new equilibrium in the isoprenoid metabolism through feedback mechanisms or other selection methods. This could favor the production of certain end products over others, thereby correcting a putative shortage. Such an effect is reminiscent of the situation in Smith-Lemli-Opitz syndrome, a rare hereditary disorder characterized by pathologically low concentrations of cholesterol. It is caused by a deficiency of 7-dehydrocholesterol reductase, the last step in the Kandutsch-Russell cholesterol biosynthetic pathway. Inhibition of HMG-CoA reductase by statins in this syndrome results in a paradoxic increase of cholester-

| *Febrile attacks, (length and severity score)†* | | | | | | |
|---|---|---|---|---|---|---|
| *Washout* | | *Second period* | | | | |
| 5 d, VAS 3 | 4 d, VAS 3 | 3 d, VAS 2 | 3 d, VAS 1 | 4 d, VAS 4 | 3 d, VAS 2 | |
| | | 3 d, VAS 3 | 6 d, VAS 7 | | | |
| 7 d, VAS 8 | | 7 d, VAS 5 | 14 d, VAS 9 | | | |
| | | 1 d, VAS 8 | 7 d, VAS 9 | | | |
| | | 9 d, VAS 7 | 6 d, VAS 8 | | | |
| | | 9 d, VAS 2 | 3 d, VAS 1 | 6 d, VAS 1 | 10 d, VAS 1 | 6 d, VAS 3 |

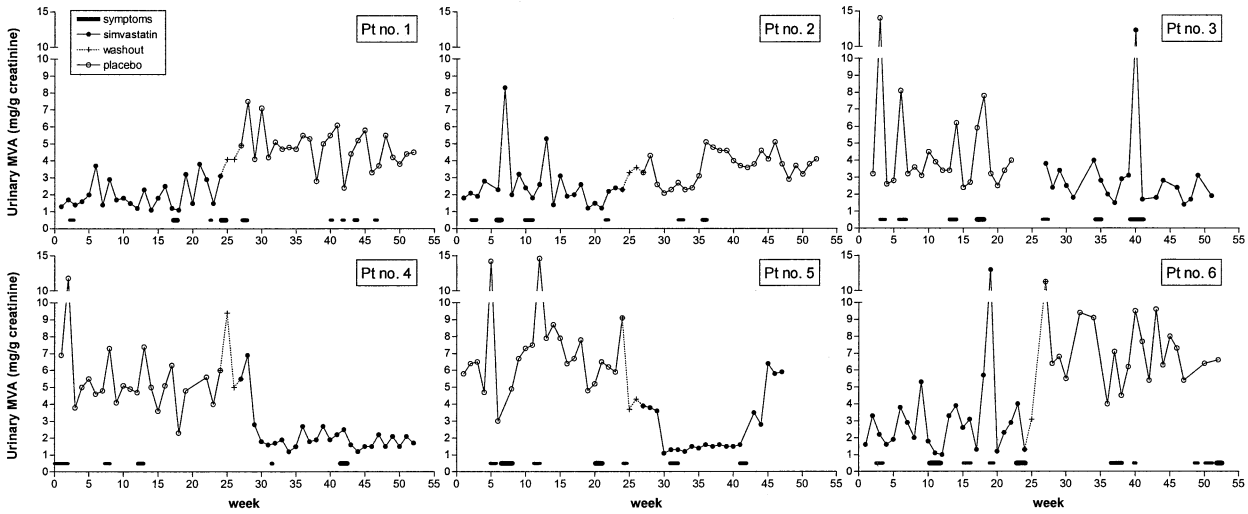


**Fig 4.** Urinary mevalonic acid (MVA) concentration in weekly collected urine samples in 6 individual patients during placebo period (*open symbols*), 4-week washout period (*crossed symbols* and *dotted lines*), and simvastatin period (*solid symbols*). Also indicated are the fever episodes of each patient (*horizontal bars*). Patient 3 omitted collection of urine samples during the washout period, and patient 5 admitted to noncompliance at the end of the study period.

ol,[15] most likely through augmentation of residual enzyme activity.

The possible benefit of simvastatin appears to go beyond the period the drug was actually used. In particular, we observed a possible carryover effect in clinical outcome parameters in patients first treated with simvastatin and then by placebo. How does this relate to the biologic action of simvastatin? The high dose of simvastatin resulted in the expected decrease in cholesterol values (Fig 3) from the normal serum cholesterol values at the start of this study. Interestingly, the possible carryover effect was not mirrored by the cholesterol concentration, because cholesterol concentrations had normalized at the end of the washout period whereas the clinical effect still persisted.

The mechanism for the observed carryover effect is not clear. It is possible that prolonged treatment with simvastatin results in a depletion of accumulated mevalonic acid, thereby restoring the balance within the isoprenoid pathway. However, this hypothesis does not seem to be corroborated by the rapid increase of mevalonic acid excretion observed in our patients after discontinuation of simvastatin. Alternatively, the simvastatin treatment has restored depleted concentrations of 1 or more isoprenoid end products, such as isoprenylated proteins, which may persist for a prolonged period.

We did not observe side effects in our patients, and this result differs appreciably from results obtained in children with severe mevalonate kinase deficiency in

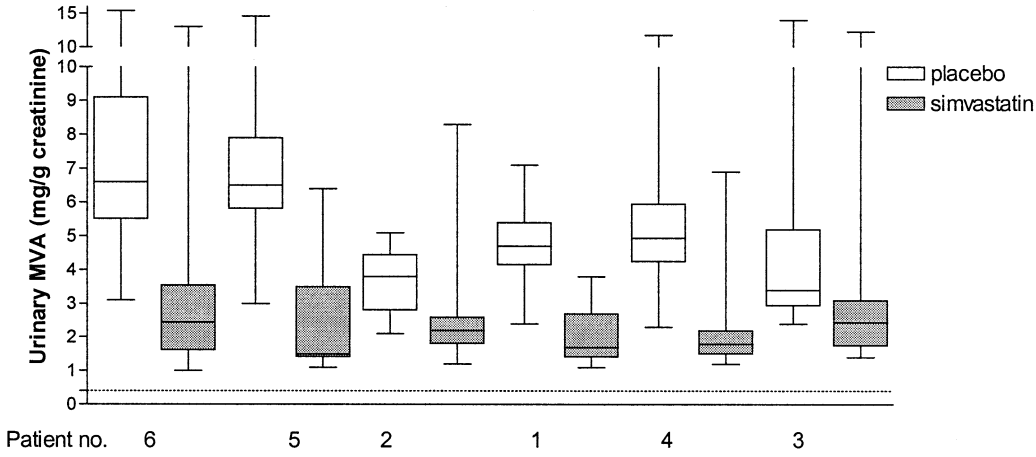


**Fig 5.** Box-and-whisker plots of urinary MVA concentration in 6 individual patients in placebo period versus simvastatin period, arranged from lowest (patient 5) to highest (patient 3) known mevalonate kinase enzyme activity (mevalonate kinase activity in patient 6 not determined). The *dotted line* represents the normal concentration detected in healthy control subjects ($0.4 \pm 0.18$ mg/g creatinine).

whom statins allegedly induced attacks.[9] Several factors might be responsible for this discrepancy. In the first place, we observed that, although it had a beneficial effect, simvastatin did not result in a complete absence of inflammatory crises. It is possible that the attacks seen by Hoffmann et al[9] were part of the "normal" phenotype of the disease and not caused by the statin. A longer treatment of the 2 children in the study of Hoffmann et al might have resolved this issue. Second, both of the children described by Hoffmann et al used supplements that exert an influence on the isoprenoid metabolism, including cholesterol, ubiquinone, and vitamin E. The resulting effect of this combination treatment on the isoprenoid metabolism is hard to predict but may be disadvantageous. A third possible explanation is the higher residual mevalonate kinase enzyme activity in HIDS compared with classical mevalonic aciduria (5.7%-11.3% versus 0%-1.5%).[9] Therefore the results of this study cannot be extrapolated to patients with classical mevalonic aciduria.

In conclusion, we describe preliminary evidence for a possibly effective treatment for HIDS in a randomized, double-blind follow-up study of 6 patients. Although our trial is small, randomized trials are clearly to be preferred over observational studies and, in our opinion, controlled studies provide the only way that any unbiased measurements of effectiveness can be made. In any case, we hope to set the stage for a larger trial, and additional clinical experience with HMG-CoA reductase inhibitors in HIDS in more patients over a longer period of time is desirable to prove its standing in clinical practice. This study again highlights the relationship between inflammation and the isoprenoid metabolism and offers additional evidence for the antiinflammatory activity of HMG-CoA reductase inhibitors.[16,17]

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