A 6-month trial of simvastatin (HMG-CoA reductase inhibitor) in the treatment of hypercholesterolaemia

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Summary

The aim of this study was to evaluate the long-term efficacy and tolerability of the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor simvastatin, over a 24-week period. Patients (108) with primary hypercholesterolaemia were clinically, haematologically and biochemically evaluated and established on a cholesterol-lowering diet. After a wash-out period free from other lipid-lowering drugs and a baseline period on placebo of 1 month each, 10 mg simvastatin was introduced at night. The dose was increased to 20 mg and 40 mg at 6 and 12 weeks' follow-up respectively if the total cholesterol (TC) level was still above 5,17 mmol/l. Follow-up took place every 6 weeks and included lipid, haematological, biochemical and clinical evaluation. A full ophthalmological evaluation was conducted at baseline and at 24 weeks' follow-up.

Overall the TC level was reduced below the baseline level by 34,3% at week 18 of follow-up and 32,5% at week 24. Patients with higher initial TC levels showed greater TC lowering in response to simvastatin than did those with lower initial TC levels. A group of 45 patients was followed up for an additional 12 weeks after the end of the trial and maintained TC reductions similar to those at the end of the trial.

Fourteen patients experienced adverse effects which were thought to be drug-related. One patient was withdrawn from the trial after developing conjunctivitis that proved to be related to the use of simvastatin. The rest of the adverse experiences were not severe enough to terminate the use of simvastatin and included gastro-intestinal tract symptoms, dizziness, conjunctivitis, pruritus and the aggravation of eczema. Aspartate aminotransferase, alanine aminotransferase and creatine kinase values were raised in a significant number of patients but no patient was withdrawn from the trial. A dose of 40 mg simvastatin was associated with a rise in the abovementioned enzymes more often than were lower doses.

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The benefit of reducing raised plasma cholesterol levels to prevent myocardial infarction (MI) has been illustrated by a number of large multicentre drug trials.[1,3] These results led to the formulation of general guidelines for the diagnosis and management of hypercholesterolaemia[4-6] in order to reduce coronary heart disease (CHD) in a number of countries.

Most persons with a cholesterol level imparting moderate or even high risk[4-6] of developing CHD can reduce that level by means of a strict cholesterol-lowering diet and other lifestyle modifications. A significant number of persons will, however, still require medication to achieve optimal cholesterol levels.

Currently available drugs employed to reduce plasma cholesterol levels show limited efficacy and are associated with troublesome side-effects, while long-term safety cannot be assured for all drugs.[7] A new group of cholesterol-lowering drugs appear to be promising for the treatment of hypercholesterolaemia, as has been shown by controlled and uncontrolled trials.[8-15] These drugs inhibit the rate-limiting enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, in the synthesis of cholesterol. When *de novo* cholesterol synthesis is reduced, the hepatocyte increases its expression of low-density lipoprotein (LDL) receptors in order to meet the demand for cholesterol. Consequently plasma LDL cholesterol (LDLC) is reduced. Low doses of these drugs will reduce plasma cholesterol effectively, and in short-term studies they seem to be safe.[8-12] Consequently in 1987 the Food and Drug Administration in the USA approved the use of the HMG-CoA reductase inhibitor lovastatin for the treatment of hypercholesterolaemia. A number of other HMG-CoA reductase inhibitors are currently under investigation for the treatment of this condition.

The aim of this study was to investigate whether the efficacy and tolerability of the HMG-CoA reductase inhibitor simvastatin during short-term studies is maintained in a once-a-day dose over a 24-week treatment period of use as a cholesterol-lowering agent.

Methods

Patient selection

One hundred and seventeen patients with primary hypercholesterolaemia, aged 18 - 65 years and with a serum total cholesterol (TC) level above 6,5 mmol/l, were selected at five South African lipid clinics to participate in the study. Exclusion criteria were a plasma triglyceride level above 4,7 mmol/l or

types I, IV or V hyperlipidaemias, and a fasting glucose level above 7,7 mmol/l; pregnant or lactating women, as well as premenopausal women who were not on effective contraception during the study, persons with a history of drug or alcohol abuse, impaired hepatic function or a history of hepatitis, patients who had had a partial ileal bypass, who had recently suffered from unstable angina or an MI, or had had coronary bypass surgery within the previous 3 months; patients who used immunosuppressive drugs were also excluded.

All participants underwent clinical examination and laboratory investigations; electrocardiography and a detailed eye examination, including slit-lamp examination by an ophthalmologist after dilatation of the pupil, as well as visual acuity testing, were also performed.

All participants gave voluntary written consent to participate in the study after a detailed explanation of the protocol and potential risks of the trial. The protocol was approved by the ethical and research committees of the universities involved.

Treatment regimen

Fig. 1 represents a flow-diagram of the drug regimen. All patients who had been on lipid-lowering drugs before the trial discontinued these drugs for a wash-out period of at least 4 weeks. This was followed by a 4-week baseline period on placebo before the start of active treatment. At entry, 8 weeks before the initiation of simvastatin, participants were placed on a lipid-lowering diet as prescribed by the Nutrition Committee of the American Heart Association.[16] The patients were seen by a dietitian at each visit to the clinic to assess diet compliance.

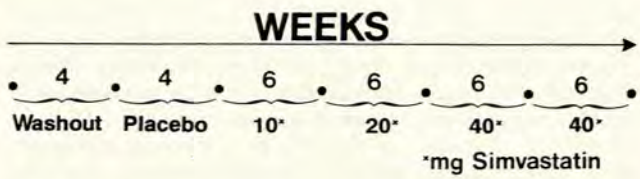

Fig. 1. Drug regimen.

Treatment was initiated with 10 mg simvastatin to be taken with the evening meal. After 6 weeks a complete laboratory evaluation was done. If the TC level was still 5,17 mmol/l or above the simvastatin dose was increased to 20 mg in the evening. For patients in whom it was 5,17 mmol/l or above 12 weeks after the initial treatment, the dose was increased to 40 mg in the evening. At 18 weeks cholestyramine could be added to the regimen if the TC level was still above 5,17 mmol/l. Subjects were monitored at 6-week intervals until each had taken simvastatin for a period of 6 months.

In addition, the dose of individual patients was adapted in response to side-effects experienced and the degree of cholesterol lowering achieved.

Clinical and laboratory monitoring

Adherence to treatment was assessed by tablet counts at each visit. Any side-effects were monitored and reported to the drug company as they occurred. The patients continued with whatever non-lipid lowering medication they had been taking before commencing simvastatin and any additional drugs taken were noted. The pulse, blood pressure and body weight were measured at each visit. If any change in lifestyle took place, it was noted. At the final visit an ECG and physical and ophthalmological examinations were conducted by the same person who had conducted the initial examination. The ophthalmological examination included a visual acuity test and a slit-lamp examination after dilatation of the pupil.

Blood for biochemical and haematological analyses was taken after a 12-hour overnight fast. The non-lipid biochemical and haematological measurements were performed using standard techniques by routine clinical chemistry and haematological laboratories. These analyses included the measurement of haemoglobin, haematocrit, white blood cells, differential and platelet counts, and total bilirubin, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatine kinase (CK), creatinine and glucose levels.

Cholesterol and triglyceride determinations were done using enzymatic methods. All centres used the same commercial analytical kits and methods to obtain comparable results. For TC determinations the CHOL-PAP-HPR enzymatic kit (Boehringer Mannheim) was used and for triglyceride determinations the neutral fat kit, also from Boehringer Mannheim, was used. High-density lipoprotein cholesterol (HDLC) was measured after precipitation of the apoprotein-containing lipoproteins by heparin-manganese chloride according to the Lipid Research Clinics protocol.[17] LDLC was calculated using Friedewald *et al.*'s formula.[18]

Statistical methods

The univariate distribution of each management was studied to detect data recording errors as well as to assess differences between centres. Sequential differences between the same measurement at the different times of follow-up were calculated for each variable and separately for each centre, to study the changes from visit to visit. The Fisher method of combining the significance levels of independent statistical tests was applied to accommodate any heterogeneity in the distributions for the different centres. This method was used to combine separate statistical tests done on the TC and LDLC results from each centre.[19]

In Figs 2 and 3 the 'box' part of the plot of the TC measurement is an arrangement of three parallel lines, the bottom, middle and upper lines representing the lower quartile (25th percentile), the median (50th percentile) and the upper quartile (75th percentile) respectively. The mean is indicated by a + sign, which is usually inside the 'box'. The mean and the median are about the same if the distribution is symmetrical. The spread of the distribution can be measured by the distance between the upper and lower quartiles, this distance being called the interquartile distance.

In Fig. 4 a bivariate plot of baseline LDLC and LDLC at 6, 18 and 24 weeks' follow-up respectively is provided. The line

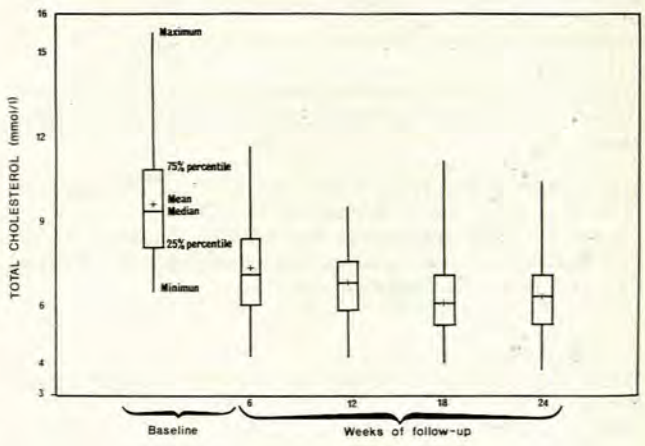

Fig. 2. Shift in the distribution of TC levels at baseline and 6, 12, 18 and 24 weeks of follow-up.

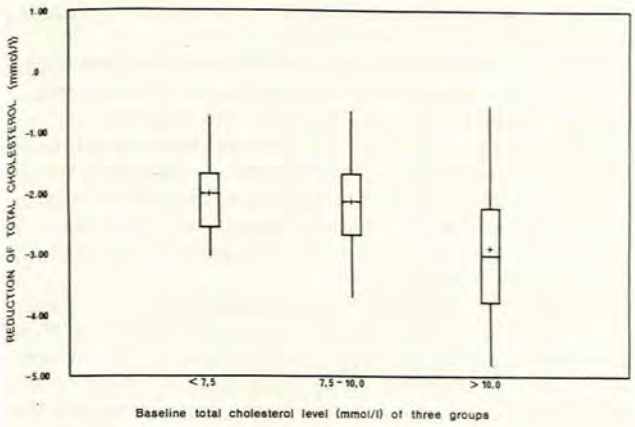

Fig. 3. Comparison of the reduction of TC levels in three groups of patients on the basis of their initial TC levels.

of no change in LDLC levels from baseline to follow-up period is indicated by a solid diagonal line. A lowering of LDLC at follow-up is reflected by observations above the diagonal line.

Results

Data for 108 of the 117 patients entered into the trial (mean age 45,3 years, range 21 - 63 years, 56 men and 52 women) were analysed (2 patients were excluded because they were outside the age range, mean triglyceride levels for 3 patients were above 4,7 mmol/l before taking the drug, mean serum cholesterol levels for 2 patients were below 6,5 mmol/l before taking the drug, 1 patient's laboratory results could not be verified, and 1 patient was lost to follow-up after taking 10 mg simvastatin for 6 weeks). The characteristics of the patients included are shown in Table I.

TABLE I. THE CHARACTERISTICS OF PATIENTS IN THE TRIAL

No.	**108**
Age (yrs) (mean) (range 21 - 63 years)	**45,3**
Males (%)	**51,9**
Patients with a history of CHD (%)*	**38,9**
Patients with ECG features of CHD (%)†	**15,7**
Patients with clinical signs of hypercholesterolaemia (%)‡	**37,0**
Patients with possible familial hypercholesterolaemia (%)¶	**15,7**

* CHD was considered to be present if a patient reported suffering from angina and/or myocardial infarction and/or had had coronary artery bypass surgery.
† ECG changes considered were Q waves and S-T segment depression.
‡ Clinical signs of hypercholesterolaemia considered were tendon xanthomas, arcus cornealis and xanthelasma.
¶ Patients with familial hypercholesterolaemia had a total cholesterol level in the high CHD risk category (> 80th percentile)[4] and a triglyceride level below 2 mmol/l as well as clinical signs of hypercholesterolaemia.

Of the 108 patients who participated in the trial, 93 followed the same dosage pattern over the study period (4 patients followed the same dosage pattern except for the last period, a further 4 stayed on a 20 mg dose for the third period and caught up again at the last period, 4 never moved on to a higher dose than 20 mg, and the remaining 3 received 10, 10, 20 and 20 mg at the four consecutive visits).

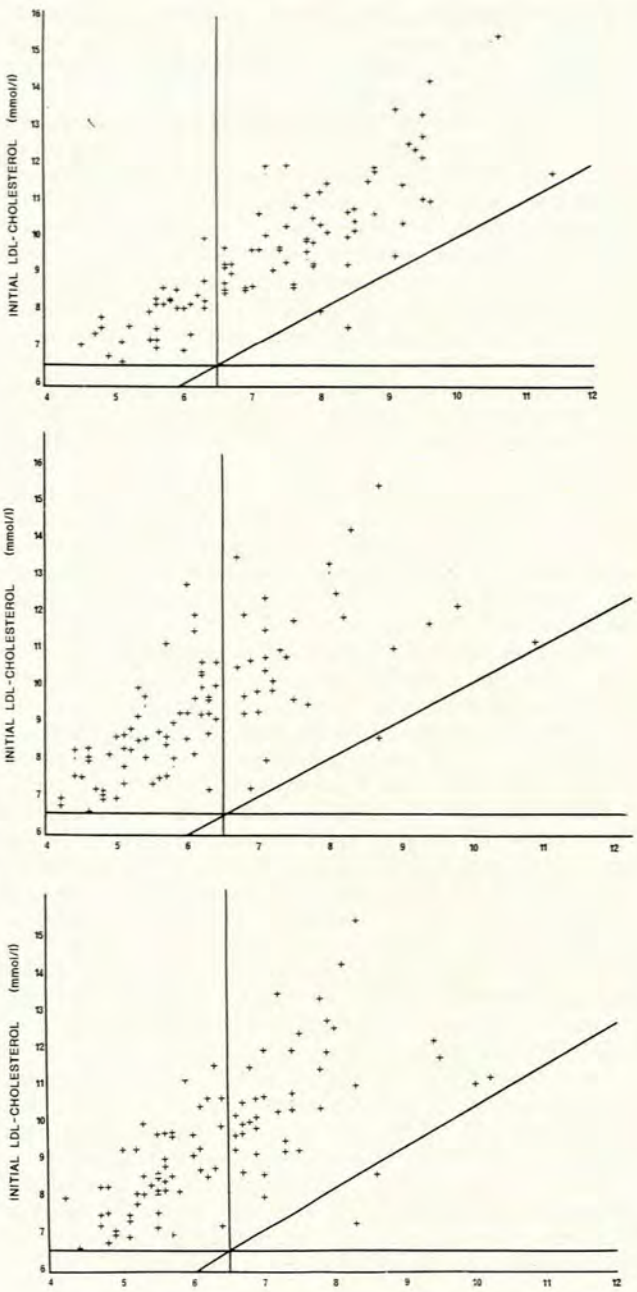

Fig. 4. Comparison of baseline LDLC levels with LDLC levels at 6 weeks (10 mg simvastatin) (top), **18 weeks (40 mg)** (middle) **and 24 weeks (40 mg)** (bottom).

The change in the distribution of TC during the use of simvastatin is shown in Fig. 2. The mean TC level (± SD) of the two baseline determinations (TC level before and after placebo period) was 9,4 ± 1,75 mmol/l. On a dose of 10 mg simvastatin the mean TC level was reduced to 7,17 ± 1,42 mmol/l, a statistically significant 23,8% reduction. At the 12th week of follow-up the dose for 104 patients was increased to 20 mg and a further reduction to a mean TC level of 6,78 ± 1,16 mmol/l was observed. Six patients' TC levels were below 5,17 mmol/l.

At the 18th week of follow-up the dose for 93 patients was increased to 40 mg simvastatin. The mean TC level was reduced to 6,2 ± 1,25 mmol/l. Twenty-three patients' TC levels were reduced to below 5,17 mmol/l. Three patients whose TC levels fell below 4,5 mmol/l on 40 mg simvastatin

had the dose reduced to 20 mg, while in 1 patient the dose was reduced to 30 mg because of side-effects. Nine patients at one centre also received cholestyramine in addition to 40 mg simvastatin at week 18 of follow-up.

At the 24th week of follow-up the mean TC level of the patients increased slightly to 6,35 ± 1,23 mmol/l. In only 16 patients was the TC level below 5,17 mmol/l. The addition of cholestyramine at the one centre did not have any observable lowering effects on TC. The mean TC level of the 9 patients given cholestyramine was 8,04 mmol/l before taking the drug and 8,02 mmol/l 6 weeks after its commencement. Overall the mean TC level was reduced by 34,3% at week 18 of follow-up and by 32,5% at week 24. A differing degree of TC lowering in response to simvastatin was found at the five participating centres. At week 18 of follow-up the lowering of TC from baseline at the five centres was 23%, 34,6%, 35,4%, 37,2% and 37,3% respectively and at week 24 it was 19,7%, 33,2%, 34,7% 35%, and 35,6%.

As there was a slight increase in the TC level at week 24 of follow-up the possibility of an 'escape phenomenon' was considered. To establish whether this had occurred 49 participants who remained on a constant simvastatin dose were followed up for a further 12 weeks after the trial had ended. No significant change in the TC level occurred.

When the degree of TC lowering on simvastatin was compared with the initial TC level by means of the general additive interactive model[20] to fit a representative line, it was found that the patients with the higher TC levels showed a greater degree of TC lowering in response to simvastatin than patients with lower initial TC levels. This is illustrated in Fig. 3, where the mean TC reduction of patients with a baseline TC of below 7,5 mmol/l was 2 mmol/l while taking 10 mg simvastatin (week 6 of follow-up). On the same dose patients with an initial TC level equal or above 10 mmol/l showed a mean TC reduction of 3 mmol/l. This phenomenon was observed at all the follow-up visits and at all the various doses of simvastatin used. The subgroup of patients with familial hypercholesterolaemia, who had a higher initial TC level than the rest of the cohort, did not show this phenomenon of greater TC lowering than the rest of the cohort.

Fig. 4 shows the overall shift of LDLC levels of all participants at weeks 6, 18 and 24 of follow-up. Mean LDLC was reduced by 28%, 32,7%, 39,8% and 38,6% compared with baseline at weeks 6, 12, 18 and 24 on simvastatin treatment.

Overall, serum HDLC and triglyceride levels were not affected by simvastatin. The responses of these two lipid fractions to simvastatin were significantly different between the five centres and could therefore not be combined.

Adverse experiences

During the course of the trial no significant changes or trends were observed in pulse, blood pressure or body weight recordings or in the results of ophthalmological examination of the participating patients.

Table II indicates the clinical adverse experiences reported by patients during the trial as well as those side-effects attributed by investigators as possibly, probably and definitely related to taking simvastatin. Reported clinical adverse experiences cover many body systems, with the most common ones being mild gastro-intestinal symptoms, manifestations of CHD, joint pains, skin conditions and eye complaints.

The conditions thought to be related to simvastatin were a variety of gastro-intestinal complaints (10 participants), skin conditions (3), dizziness (1), and conjunctivitis (1).

The gastro-intestinal conditions reported were nausea, heartburn, abdominal discomfort, flatulence, constipation and loose stools. Many of these complaints were transient or relieved by taking divided or reduced doses of simvastatin or by ensuring that the drug was taken after meals.

The skin conditions thought to be related to simvastatin were pruritus, bruising and the aggravation of mild eczema to the point that topical steroid treatment was required.

One patient complained of dizziness and concomitant nausea when the simvastatin dose was increased. Divided doses allowed a gradual increase to 30 mg simvastatin. This patient's symptoms persisted at a dose of 40 mg, which had to be reduced to 30 mg. At the end of the trial the symptoms recurred and treatment was terminated.

One patient complained of conjunctivitis. The patient developed redness and itchiness of the eyes after taking 40 mg simvastatin for 22 days (total time on the drug was 14 weeks and 1 day). Withdrawal of the drug cleared symptoms in 3 days. Rechallenging the patient with the drug on two occasions precipitated the same symptoms after 3 days and 24 hours respectively. The patient was withdrawn from the trial.

Seven patients suffered serious adverse cardiovascular effects during the trial. None of these was thought to be related to the use of simvastatin. Six of these patients had a history of CHD before entering the trial. Three patients suffered angina during the trial, 2 patients developed crescendo angina necessitating coronary artery bypass grafts, and 2 patients were found to have an ECG pattern of inferior MI (Q waves in leads II, III and AVF). One of these patients was admitted to the coronary unit on day 24 on a dose of 10 mg simvastatin. Angioplasty was performed and he was symptom-free from the 10th week of the trial. The second patient, with an ECG pattern of inferior MI at week 24, had no previous history of CHD and suffered no signs or symptoms suggestive of MI during the course of the trial.

With the exception of the liver enzymes and CK, no significant trends were found in the haematological or biochemical measurements on the blood samples of the patients during simvastatin treatment. Two patients became hyperuricaemic and 2 patients maintained a raised urate level throughout the trial. One patient, who was a regular blood donor, developed hypochromic anaemia and 1 patient developed thrombocytopenia during the course of the drug trial.

The plasma serum enzyme levels were analysed with respect to the normal laboratory range for each centre. The AST levels were raised in 7,2%, 4,1%, 2,1% and 5,2% of participants at 6, 12, 18 and 24 weeks follow-up. A rise in the ALT level in 5,2%, 10,3% and 14,6% of participants was observed at 6, 12, 18 and 24 weeks of follow-up. CK levels rose in 7,2%, 2,1%, 10,3% and 5,2% of participants above the upper limit of normal at the same periods of follow-up. In 6 of these patients the raised CK level was associated with high levels of physical activity. In all cases these enzyme levels had been normal after the wash-out period.

No participant was withdrawn from the trial due to a threefold or greater increase in AST, ALT or CK. For ALT in particular, and to a lesser degree for AST and CK, a tendency to higher levels within the normal range of values for a given centre was observed at all centres. This was more marked in patients on a 40 mg/d dose of simvastatin than in patients at lower doses.

Discussion

The degree of TC (34,3%) and LDLC (39,8%) lowering in this trial is consistent with other reported results on the use of simvastatin[21–23] and lovastatin.[24–28] At baseline 90,9% of participating patients were in the high CHD risk category because of their TC levels,[4] while at the end of the trial only 24,2% fell into this category. Such reductions in TC and LDLC levels

statin and cholestyramine, reducing the fraction of simvastatin absorbed. This may also happen if simvastatin or any active metabolite undergoes enterohepatic recycling.

Simvastatin was tolerated very well in this study (Table II). Only 1 patient withdrew from the study. She suffered from conjunctivitis, which was clearly induced by simvastatin, as was indicated on two occasions by rechallenge. Other adverse experiences ascribed to simvastatin were a variety of gastrointestinal symptoms, some transient, while others were relieved by divided or reduced doses of simvastatin. Dizziness and aggravation of eczema were also observed in this study. Some adverse experiences reported in other simvastatin and lovastatin trials,[21-23,29] such as headache and blurred vision, were not experienced by patients in this trial.

As in other reported studies,[21-29] increases in hepatic transaminases, particularly serum glutamate pyruvate transaminase, were observed. These increases were small and did not lead to any participants being withdrawn from the trial. Similar findings have been reported for most other lipid-lowering drugs.[7] The long-term effect that the continued use of simvastatin has on the liver when transaminase levels are elevated is not known. For this reason patients taking simvastatin should have their hepatic function monitored at regular intervals. Consideration should be given to discontinuing the drug if the increase is persistent. In this study higher doses of simvastatin were associated with greater increases in these enzymes as was observed with the lower 10 mg dose.

Although no patients complained of muscle pain or weakness, 10 patients were found to have raised CK values; 6 of them reported participating in regular heavy physical exercise. No patient on simvastatin had clinical manifestations of rhabdomyolysis. In view of reports of rhabdomyolysis in patients taking lovastatin[30-32] in combination with gemfibrozil, niacin and cyclosporin, CK levels in patients on simvastatin should be monitored carefully and symptoms of muscle dysfunction should be sought.

When lovastatin was administered to a variety of experimental animals in doses greatly exceeding those used for human therapy, cataracts developed.[33] However, ophthalmological examinations formed an important part of this and other trials.[10,34] To date no data published or results from this study indicate any effect of lovastatin or simvastatin on the human lens,[8,29] but annual slit-lamp examinations are none the less recommended by the drug manufacturers.

We found that a daily dose of 10 mg simvastatin reduced the TC level by 23,5% and the LDLC level by 28%. Mol *et al.*[22] reported similar reductions (24,8% for TC and 27,2% for LDLC) on the same dose. Berger *et al.*[23] pointed out that a dose of 20 mg lovastatin was required to reduce TC levels by 25% and LDLC levels by 30% in most studies. In contrast, these results show that only 10 mg simvastatin is required to reduce TC and LDLC by a similar margin to that achieved by 20 mg lovastatin. The findings of Illingworth *et al.*[35] also suggest that simvastatin may be more effective than lovastatin in reducing TC. This could possibly be explained by the fact that simvastatin has an affinity for HMG-CoA reductase that is 13 000 times more than that of the natural substrate, while the affinity of lovastatin is only half (6 250) that of simvastatin.[8] This possible relationship between affinities for the enzyme and clinical potency may have a bearing on adverse effects related to these drugs. In this study the adverse effects, particularly those on hepatic transaminases, were found to occur more commonly at higher doses.

The design of the present study has limitations in that it was not a randomised controlled trial and therefore effects ascribed to the use of simvastatin could be questioned. In other randomised controlled trials with simvastatin[11-15,20] and lovastatin[34-37] similar effects to the ones reported in this study could be shown to be associated with the use of these drugs.

Simvastatin represents a promising new HMG-CoA reductase inhibitor that reduces TC and LDLC levels. Few adverse effects were reported for the duration of this study, and for most patients a single dose after the evening meal was sufficient to achieve a substantial lowering of cholesterol levels, which may lower CHD risk. Possible detrimental side-effects of lifelong use of simvastatin still need to be determined.

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