Research Assignment

Treatment of Hypercholesterolaemia with Simvastatin.

Evaluation of Herbs and Nutrients for Adjunct or Alternative Treatment.

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1 Introduction

The aim of this assignment is to evaluate treatment of hypercholesterolaemia with simvastatin and adjunct treatment with nutrients or herbs. One nutrient, fibre, is evaluated as a possible alternative treatment option for hypercholesterolaemia to simvastatin. At the end a general treatment recommendation is given.

2 Conventional Drug Therapy with Simvastatin

2.1 Pharmacology of ingredients

Simvastatin belongs to HMG-CoA reductase inhibitors (or statins), which competitively inhibit HMG-CoA, an enzyme that is rate limiting in cholesterol synthesis. Lowered cholesterol synthesis leads to increased clearance of LDL-cholesterol (LDL-C) from the blood (Bryant & Knights, 2007).

Additionally, Statins show anti-atherosclerotic properties such as decreased platelet aggregation, reduction of inflammatory processes and vasculoprotective properties. (Bryant & Knights, 2007; Kleemann & Kooistra, 2005)

Simvastatin is a pro-drug and is metabolized in the liver by CYP3A4 (part of cytochrome P450) to its active form in the first pass metabolism.

It can lower total cholesterol (TC) by 10% - 45% and increase HDL-cholesterol (HDL-C) by 2 – 13% (Bryant & Knights, 2007; Edwards & Moore, 2003).

A double-blind randomized placebo-controlled trial (DBRPC trial) of primary hypercholesterolaemic children at multiple centres showed that simvastatin statistically significantly lowered (TC) and LDL-C by 23.9% and 31.4% after 8 weeks and 30.9% and 40.7% after 48 weeks. However no significant changes in HDL-C levels were reported (de Jongh et al, 2002). A more recent DBRPC trial with children using pravastatin showed similar results (Wiegeman et al, 2004).

2.2 Main Indications and costs

Simvastatin is used in combination with dietary treatment for hypercholesterolemia and indicated in patients with high risk of developing coronary heart disease, including patients with past events of stroke, cerebrovascular or peripheral vessel disease, severe angina pectoris or diabetes. (MIMS, 2007).

Simvastatin is given 10 mg daily before bedtime, titrated monthly as needed up to 80 mg/day (Bryant & Knights, 2007).

The dispensed costs and the costs to the patient after the government subsidy are given in the table below on a monthly basis (PBS, 2008).

Tablet Strength	*Dispensed Cost per month*		*Cost to patient per month*	
Statin:	Generic in $	Brand in $	Generic in $	Brand name in $
5 mg	22.66	23.99	27.30	28.63
10 mg	29.23	30.56	31.30	36.63
20 mg	39.64	40.97	31.30	36.63
40 mg	54.65	55.99	31.30	36.63
80 mg	76.17	77.50	31.30	36.63

2.3 Safety Issues

2.3.1 Contraindications

Simvastatin is contraindicated in pregnancy and lactation, women of childbearing age unless they use effective contraception and in active liver disease (MIMS, 2007).

Bryant & Knights (2007) also mention the following contraindications:

- pre-existing liver / renal impairment;
- Severe intercurrent illness (infection, trauma);
- Prior to major surgery;
- Pregnancy.

2.3.2 Interactions

The main interaction with simvastatin are related to increased risk of myopathy if used in conjunction with certain antibiotics, anti-fungals or large doses of grapefruit juice (due to CYP3A4 interactions) or when using lipid lowering fibrates or niacin (Bryant & Knights, 2007; MIMS, 2007).

Inducers of CYP34A such as barbiturates, carbamazepine, phenytoin & griseofulvin cause a reduction of plasma level concentration of simvastatin (Bryant & Knights, 2007). Simvastatin showed to increase the effect of warfarin (MIMS, 2007).

2.3.3 Adverse Reactions

Bryant & Knights (2007) list following adverse reactions:

- GIT discomfort, headaches, insomnia & dizziness;
- ↑ hepatic transaminase levels;
- Potential of myopathy with possible progress to rhabdomyolysis & renal failure.

3 Integrative Approach - Possible Interactions and Potentiations with Natural Medicine

3.1 Nutritional

3.1.1 Fish Oil

- In a double blind, randomized, placebo controlled (DBRPC) studies, hyperlipidaemic patients on stable statin therapy showed that, addition of fish oils or omega-3-acid ethyl ester synergistically reduced triglyceride levels more than statin treatment only (Davidson et al, 2007; Durrington et al, 2001).
- A recent meta-analysis concluded that treatment with omega-3 fatty acids was a useful and safe adjunct to statin therapy to lower triglyceride levels (Nambi & Ballantyne, 2006).

3.1.2 Co-Enzyme Q10

- A meta-analysis concluded that there is some evidence that the reduction of CoQ10

levels in statin treated patients is the reason for the development of myopathies, but also concluded that treatment with CoQ10 was safe (Marcoff & Thompson, 2007). Noteworthy is that one of the authors received research support from as well as having own stocks in the pharmaceutical companies Merck, Pfizer and Schering-Plough.

- A small study of 18 patients with hypercholesterolemia, of which 8 exhibited muscle symptoms, concluded that statin drug related myopathy is associated with mild decrease in muscle CoQ10 concentration. (Lamperti et al, 2005).

- In a DBRPC clinical trial 32 subjects using statin treatment and reporting myopathic symptoms were either given 100 mg CoQ10/day or Vitamin E. 16 out 18 patients in the CoQ10 group reported improvements. In average CoQ10 subjects showed a decrease of 40 % of pain severity and 38% pain interference. No change was evident in the control group. (Caso et al, 2007).

3.1.3 Policosanol

- A meta-analysis of policosanol research showed that the human studies showed a safe and effective action of policosanol. Efficacy was considered similar to statin drugs, including simvastatin. However the author also acknowledged that most of the research was done in Cuba using Cuban policosanol (Janikula, 2002).
- Two recent DBRPC trials have shown that the effect of policosanol (not of Cuban origin) on cholesterol levels was statistically not significant when using the same or higher dosages as in previous trials (Berthold et al, 2006; Dulin et al, 2006).
- Further research is necessary to make a definite statement.

3.1.4 Red Yeast Rice

- A meta-analysis of 93 trials using 3 different red yeast rice preparations (2 of them being a combination with other herbs) showed that all 3 of them lowered total cholesterol levels and 2 of them were equally effective as the tested statins. (Liu et al, 2006).
- Red Yeast Rice can have side-effects and is contraindicated in liver disease. Furthermore

no long term safety data is available yet (IMgateway, 2008).

3.1.5 Vit B_3 (Niacin)

- Niacin has been used since the 1950s and studies show that extended release niacin reduces TC and LDL-C significantly while raising HDL-C levels. (Braun & Cohen, 2007).
- Slow release niacin used in conjunction with statins in a 1053 patient trial that was prospective, observational and mulitcentred showed to be generally well tolerated and safe. Major complaints were flushing and sometimes pruritus, upper abdominal pain and nausea. HDL-C increased and triglycerides decrease significantly. LDL-C and TC changes were modest (Birjmohun et al, 2007).

3.1.6 Probiotics

- Various in vitro studies showed the potential of probiotics to reduce cholesterol (Brashears et al, 1998; Buck & Gilliland, 1994).
- There seems to be benefit of probiotics in reducing cholesterol levels depending on the strain of probiotics used but a recent systematic review highlights that a conclusive judgement is not possible (Lion, 2007).

3.1.7 Plant Sterols

- A review of studies concluded that sterols added to the diet are more effective than doubling statin medication. 2 g / day of sterols cause usually approx 9% decrease in LDL cholesterol. Sterols were added to margarine, their use was considered safe and absorption of lipid soluble vitamins

seemed to be unaffected except for beta-betacarotenes. It was concluded that this could be remedied by increasing intake of fruit and vegetables (Katan et al, 2003).

- A DBRPC study on 73 subject over 8 weeks with sterol enriched orange juice found that the test subject consuming the equivalent to 2 g sterols/day showed a 9.4% decrease in LDL-C and 6% increase in HDL-C, however comparing HDL-C increases between placebo and study group showed no significant difference. The tabular presentation of the data was not very clear. (Devaraj et al, 2004).
- The above review and the study were sponsored by corporations that have vested interests in positive outcomes for plant sterols.

3.1.8 Soy Protein

- A meta analysis found that soy has some lipid lowering effects, especially if using soy-protein that is high in isoflavones as determined in a meta-analysis (Zhuo et al, 2004).
- A meta-analysis of 11 trials found that soy isoflavones significantly decreased TC by 1.77% and LDL-C by 3.58%. The amount of soy necessary to be eaten was approx. 230 g tofu or 2 glasses of soymilk daily (Taku et al, 2007).

3.2 Herbal

3.2.1 Cynara scolymus

- In vitro tests suggest that Cynara inhibits the synthesis of cholesterol (Mills & Bone, 2001).
- Cynara has hepatoprotective, hepatotrophorestorative, choleretic,

cholagogue, bitter tonic and hypocholesterolemic actions and clinical data from uncontrolled trials from 1936 to 1994 showed a capacity to reduce cholesterol/triglyceride levels in a range from 5% to 45% (Bone, 2003).

- More recent studies have sometimes been not quite conclusive but a German double-blind, randomized, placebo-controlled showed a decrease in LDL-cholesterol (Braun & Cohen, 2007).

3.2.2 Garlic

- Meta analyses and systemic reviews show ambivalent results when using garlic to lower cholesterol (some showed superiority to placebo, some not) which could be attributed to dosage and form of garlic preparations (Rahman and Lowe, 2006; Banerjee & Maulik, 2002).
- One meta –analysis (Stevinson et al 2001) found that garlic was superior to placebo treatment, however the reduction was modest.
- An open, non placebo controlled trial with 5 g raw garlic/day on 30 volunteers for a period over 42 days achieved a total cholesterol reduction of 11% and an increase of 10% in HDL-cholesterol (Mahmoodi et al, 2006).
- The evidence points to fresh garlic as a complimentary medicine for lowering blood cholesterol.

3.2.3 Commiphora mol mol

- The ingredient of interest is the oleo-gum-resin guggul (Braun & Cohen, 2007).
- The results of 6 randomized trials, 2 of which were placebo controlled, suggest that total serum cholesterol could be reduced ranging from 10% to 27% compared to baseline levels (Thompson Coon & Ernst, 2003).
- A DBRPC study with 103 subjects found that guggulipid in 1000 mg & 2000 mg doses given three times daily resulted in increased levels of LDL-cholesterol but 6 patients complained about sensitivity rashes (Szapary et al, 2005).
- Further research is necessary to establish a definite action.

4 Fibre as a Possible Natural Therapy Alternative

4.1 Efficacy

Water soluble fibre includes gums, mucilages, & most pectins contained in oat bran, psyllium, barley, fruit etc. whereas cellulose and lignins are non-soluble fibre (Williams & Schlenker, 2003; Jones, 2002).

Water soluble fiber has lipid lowering properties thought to be due to increased faecal bile acid excretion & interference with bile acid re-absorption. (Williams & Schlenker 2003; Jones, 2002). A trial measuring the level of α-HC (a marker of bile acid synthesis) found that 8 hours after consumption of oat bran containing 11 g β-glucan the level of α-HC went up significantly, meaning that the bile acid synthesis went up as well. (Andersson et al 2002).

Oat bran contains beta-glucans that are known for sequestering bile acids (Kohlmeier, 2003; Williams & Schlenker, 2003).

Thirty-six overweight men aged 50–75 y (normal TC & LDL-C) were randomly assigned to consume daily for 12 wk either oat or wheat cereal providing 14 g dietary fibre/day (= 5.5 β-glucan). Diet control was a 4 day food intake diary at baseline and during the final week, no other dietary modifications were implemented The recorded reduction in LDL-C and the TC:HDL-C ratio were 2.5% and 6.3% in the study group. In the control group the LDL-C increased by 8.2% and TC:HDL-C by 12.2%. There was some inconsistency regarding the statistical significance, which could be due to the study sample size (Davy et al, 2002).

Pins et al (2002) conducted a similar study, with 88 subjects, all of them with hypertension (LDL-C & TC mildly elevated). Study subjects consumed either oat or wheat cereal for 12 weeks. No other dietary modifications were implemented in the double-blind randomized trial and diet control was a 3 day food record at baseline and during final week of study. The patients continued to take the blood pressure medication. The results showed that TC and LDL-C dropped by 15% and 16% in the oat group but only 3.5% and 4.4% in the wheat group. The statistical difference between the groups was considered significant.

Both studies were financed by the producers of the oat cereal product, which could have influenced the reporting.

Psyllium is often used as adjunct to low fat diet. A cholesterol lowering effect is to be expected after approx. 8 weeks (Braun & Cohen, 2007).

In a DBRPC trial over 26 weeks 248 female & male subjects (LDL-C and TC were mildly elevated) were given either 2 sachets of metamucil (= 5.1 g psyllium) following the AHA step I diet (limited fat & cholesterol) or cellulose. Blood samples were taken at the beginning and throughout the trial in regular intervals. In the test group TC and LDL-C levels reduced by 2.1% and 2.9%. This was reported as a significant difference of 4.7% and 6.7% compared to the cellulose group (Anderson et al, 2000). The study size was good, so the results can be considered reliable.

A study of 63 subjects (mainly female, TC mildly elevated, LDL-C still normal) found no significant influence of psyllium consumption and cholesterol levels. (Van Rosendaal, 2004). This study was not financed by a corporation with interest in the product tested. However, the fibre was only administered once a day, whereas in other studies, fibre was given 2 to 4 times a day. The dietary regimen of these patients is not quite clear, as some of them were given diets high in insoluble fibre beginning 1 month before start of trial. Furthermore the study did not have a control group.

A small study with 20 patients with DM II (mildly elevated TC & LDL-C) showed that subjects taking 14 g of psyllium husks divided over 4 doses throughout the day showed that TC significantly decreased by 7.7% and LDL-C by 9.2% after 2 weeks of psyllium husks. However this trial did not have a control group. (Sierra et al, 2002).

Morya et al (2005) conducted a DBRPC study with 68 male & female subjects on statin treatment (TC & LDL-C considerably elevated). 5.1 g psyllium tds and 1 statin tablet (10 mg) nocté was compared to a placebo tds and 1 statin tablet wither 10 mg or 20 mg nocté. After 8 weks TC fell by 26% in psyllium/statin group compared to 24% in 20 mg simvastatin group. The drop in LDL-C was equal in both groups. Their study showed that a 10mg statin plus psyllium could achieve about the same results as 20 mg statin treatment. However, the

statistical significance in this trial is questionable, which could be due to the small size in each group (n=23 or n= 22).

In another study, low (0 g), medium (3 g) and high (6 g) β-glucan level diets were given to 25 subjects (TC and LDL-C mildly elevated) at randomized succession (Latin-Square Design) for 5 weeks for each diet after an initial 2-week base diet period. Results showed that the high β-glucan diet resulted in significant decreases in TC (10%) and LDL-C (17.4%) levels (Behall et all, 2004). This was the only researched study with a tightly controlled diet (subjects ate under supervision or had take-home food packs). In other cases researchers relied on food diaries etc. which are more open to errors and could affect study outcomes.

4.2 Adverse Effects of Fibre

- Bloating and flatulence are common complaints (Behall et al, 2002)
- In a study involving 20 subject that took 14 g fibre per day for 6 weeks, blood levels for Calcium, Phosphorus, Sodium, Potassium, Magnesium, Iron, Vitamin A and Vitamin E were not significantly changed between baseline and after 6 weeks. (Sierra et al, 2002).

4.3 Costs

- If using Psyllium husks:

º Dosage: 4 – 5 g of psyllium husks in water 3-4 times per day, followed by glass of water (Braun & Cohen, 2007)

º 500 g of Bonvit Psyllium Husks cost approx. $9.96 (RRP) → $0.01992/g

º Cost per day: 20 g x $0.01992 = $ 0.40/day → $11.95/month

- If using oats:

º Study using oat cereal with approx. 6.23 g soluble fibre/day. 75 g Quaker oatmeal contains approx. 3.25 g soluble fibre (Pins et al, 2002) → 100 g oat meal or rolled oats = 5.42 g soluble fibre → 114.94 g of rolled oats daily

º Price of Oats: 1 kg = approx. $ 5.70 → costs = approx. $0.65/day → approx. $19.50/month

4.4 Conclusion

In order to be a true alternative the natural therapy alternative should have similar or better efficacy in a similar or better time frame with similar or less adverse reactions.

Fibre certainly has less severe side effects than simvastatin and from that perspective is a preferable treatment option.

Changes in cholesterol levels become effective after 4 – 6 weeks when increasing the fibre intake (Braun & Cohen, 2007; Behall, 2002). Medication with Simvastatin takes approx. 4 weeks to take effects (Medscape, 2008). Both treatments are similar in onset of their effect.

Comparing the costs, fibre is approx. 28% (oats) – 56% (psyllium) cheaper. However, the patient might find it challenging to eat > 100g of oats / oatmeal every day.

In studies Simvastatin showed to reduce TC by approx. 25 % and LDL-C by approx. 34% in average (Edwards & Moore, 2003). Looking at the studies anlysed above, fibre has the potential to reduce mildly elevated TC and LDL-C levels at best by 10% and 17.4 % in conjunction with a low fat diet (Behall et al, 2002)

It is important to mention that most studies examining the benefits of fibre in lowering cholesterol were financed by the manufacturers of fibre products or involved parties that had a vested interest in positive study outcomes. This doesn't mean that the results are wrong or that fibre is not beneficial, but could have skewed some of the reporting towards more favourable statements.

Overall fibre has a good potential as an adjunct therapy together with diet, but cannot be used alone to replace treatment with Simvastatin.

5 Recommendation for Treatment Strategy

5.1 Discussion

A good adjunct therapy should have established benefits and little or no side effects. From this perspective policosanol, guggulipids and red yeast rice are not good recommendations. Although niacin has well established benefits, the side effects can be still quite substantial (hot flushes, rashes etc.).

As outlined above fibre is a safe and low cost adjunct to simvastatin.

As assistance in lowering levels of triglycerides as well, fish oil is a good complement to statins. The dosage is 4 mg of omega-3 daily (Davidson et al, 2007). However, it has to be noted that in the trials mentioned earlier the patients were also following a low fat diet, which is likely to have influenced the results positively.

Garlic has shown to lower blood cholesterol even if the results are modest (Stevinson et al, 2001). As an adjunct therapy it would be beneficial if the patient does not object to the odour. As with fibre, garlic is not expensive and is safe. .

A study with 66 hyperlipidaemic patients combined various dietary cholesterol-lowering changes over a period of 12 months such as reduction of saturated fats and cholesterol, inclusion of 1.0 g plant sterol (as margarine), 10 g soluble fibre, 22.5 g soy protein and 23 g of whole almonds (Jenkins et al, 2006). The results showed a statistically highly significant mean reduction of 12.8% in LDL-C. However, 17% of the subjects left the study pre-maturely and cholesterol reduction was very closely linked to compliance. This study shows the beneficial effect of diet however stresses the problems of compliance often found with dietary changes if they are too radical.

5.2 Recommendations to implement:

- Take 2 fish capsules twice daily with meals
- Incorporate approx. 3 cloves of raw garlic (bruised or crushed) into the diet daily
- Take 4-5 g psyllium husks in water three times per day
- Follow a diet that is similar to the American Heart Associations recommendations (AHA, 2008)

  - Reduce total fat to 25-30% of total kilojoule intake, with saturated fat being < 7%, and cholesterol less than 200 mg per day.
  - Have approx. 15% protein per day, including some soy protein
  - Carbohydrates should be from whole grains, fruits and vegetables
  - Include moderate physical exercixe daily

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