Adverse side effects of statins in the oral cavity

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Abstract

Increased plasma levels of cholesterol are high risk factors of cardiovascular disease. Statins are drugs that inhibit cholesterol synthesis at both pancreatic and extrahepathic levels, being the treatment of choice for hypercholesterolemia.

Objective: To analyze the side effects of statins in the mouth cavity, and to analyze the symptoms after interruption of the treatment.

Design: Observational study, preliminary.

Material and methods: Patients aged 50-70, diagnosed with hypercholesterolemia and undergoing treatment with statins, referred from their primary care physician to the dentist's office. Anamnesis over oral symptoms was performed in the first visit. Statin treatment was discontinued, followed by lab tests and control visits seven and fifteen days later. We monitored the improvement and/or remission of oral symptoms. Statin treatment was resumed, sending out a report of the patient evolution to the PCP. Symptoms were registered in sheet specially designed for the study. Exclusion criteria: patient refusal, use of drugs for dry mouth treatment, Sjögren's syndrome.

Results: n=26 patients. Dry mouth patients: improvement in 17 out of 23 patients (88.5%). Itchiness: 6 out of 15 cases improved (57.7%). Bitterness: improvement in 13 out of 14 patients (53.8%). Cough: improvement in 11 out of 12 patients (46.1%).

Discussion: A high percentage of oral symptoms are associated to treatment with statins. There is a marked improvement after temporary interruption of the treatment. Little is known regarding the side effects of oral treatment with statins. This preliminary study includes a relatively small number of patients. The design of experimental treatments will be required to establish a true correlation between statin treatment and oral symptoms.

Key words: *Hypercholesterolemia, statins, oral symptoms.*

Introduction

Dislipemia is an alteration of the lipid metabolism that is characterized by the increase of one or more lipid fractions in blood plasma.

The two main circulating lipids are triglycerides and cholesterol, which are obtained by ingestion or endogenous synthesis in the liver. Their ingestion is an essential component of a normal diet, because of their energy content and their role in organ and tissue structural support, as well as synthesis of hormones and neurotransmitters (1).

Plasma lipids are associated to protein particles, forming lipoproteins. Lipoproteins obtained via intestinal absorption move in structures called chylomicrons. Chylomicrons bound to lipoproteins of very low molecular density (VLDL) deposit lipids or fat on the adipose and muscular tissue, releasing fatty acids used for storage and energy transformation.

Simultaneous to the process of intestinal absorption, intestinal cells synthesize lipid structures of different densities. Depending on their composition, these particles are VLDL (very low density lipoprotein), LDL (low density lipoprotein) and HDL (high density lipoprotein).

LDL particles carry cholesterol to the tissues; when cholesterol levels in blood are high, there is risk of cardiovascular disease (ischemic cardiopathy, vascular brain damage or peripheral vascular disease). On the other hand, HDL particles transport cholesterol to the liver; this is considered a protective factor in cardiovascular disease.

The main types of dislipemia are:

-Hypertriglyceridemia: increase in plasmatic triglycerides.

-Hypercholesterolemia: increase in plasmatic cholesterol.

-Mixed dislipemia: increase in triglycerides and plasmatic cholesterol.

The different types of dislipemia can be classified regarding their ethiology:

-Primary: due to an alteration of lipid metabolism; they can be hereditary.

-Secondary: they are due to illness or drug use, e.g. diabetes mellitus, hypothyroid syndrome, alcoholism, treatment with ß-adrenergic blockers, etc.

The term dislipemia is used when total cholesterol in blood is over 200 mg/dl and triglycerides are over 160 mg/dl.

The prevalence of hypercholesterolemia in Spain varies among regions. It is estimated between 14% and 20% of adult population ages 18-75. Depending on the source, pathological levels are considered when cholesterol is over 200 or 250 mg/dl (1-8); there are 5-6 million cases in Spain (5).

Hypercholesterolemia can be regarded as high among the population of Spain. 18% people aged 35-64 (18.6% men, 17.6 % women) have blood cholesterol levels equal or over 250 mg/dl, and 57.8% (56.7% men and 58.6 % women) equal or over 200 mg/dl (4). In women, cholesterol levels in blood correlate with age; however, that does not happen in men (4).

Strikingly, between 12 and 15 million dislipemia patients in the USA are undergoing treatment with statins, and there will be another 35 million in the near future (3).

Dislipemia treatment

Healthy life style

Dislipemia treatment is based in the acquisition of a healthy life style, which is targeted towards the reduction of cardiovascular disease. These are some of the habits:

- Quit smoking.
- Reduce alcohol uptake to less than 30 g/day for men and 20 g/day for women. It must be totally avoided in cases of hypertriglyceridemia.
- Keep an appropriate weight. Hypocaloric diet will be recommended for weight excess, and the progressive reduction of fat and cholesterol to less than 300 g per day.
- Appropriate aerobic exercise adapted to the needs of the patient (e.g. walking at least 30 minutes every day).
- Fat-reduced diet.

If the dislipemia persists after a period between 3 and 6 months following these guidelines, pharmacological treatment is required (2).

Pharmacological treatment

Statins: The mechanism of action of statins consists of the inhibition of cholesterol synthesis in both the liver and extrahepatic tissue, therefore decreasing total cholesterol (TC) and cLDL (6). They are less potent on cVLDL levels and triglycerides (TG). They can induce modest increases of cHDL levels.

A non-comprehensive list of available statins (by order of appearance in the market) includes lovastatin, simvastatin, pravastatin, fluvastatin and atorvastatin. Their pharmacological effect is dose-dependent, reaching a plateau at high doses. Statins are prescribed one dose/ day, and taken at night, because maximal cholesterol synthesis occurs in the AM. In conclusion, this is the treatment of choice in the treatment of hypercholesterolemia (9).

Fibrates: They reduce the synthesis of cholesterol and enhance its elimination in the bile. They increase the catabolism of TG (6), thus decreasing their levels, and also increase cHDL. They show lower efficacy on cholesterol and cLDL than statins. They are useful in mixed dislipemia, in which hypertriglyceridemia is dominant.

Resins: They interfere with the absorption of bile acids in the intestine, increasing the conversion from hepatic cholesterol to fat (2). They diminish the levels of cLDL (to a lower extent than statins), but they can increase the levels of TG. They do not constitute a treatment of choice in dislipemia.

Ezetimibe (2,6): It selectively blocks cholesterol absorption and vegetable sterols in the jejunum. It does not affect the absorption of TG or liposoluble vitamins. It also induces an average 15% decrease in cLDL levels in monotherapy,

and combination with statins further decreases them an additional 15-20%. To our knowledge, there are no published studies on its effect on cardiovascular-related mortality, and its safety is unknown in short- and long-term.

Adverse effects of statins

Statins induce an average 26% reduction of the risk of cardiovascular disease (angina, stroke, ictus, etc.), but they are also related to severe adverse effects (AE). To our knowledge, no studies have addressed the oral AE of statins despite of the abundance of references in the literature about other statin-induced AE (Medline, Cochrane).

Silva et al. described that in 1000 patients following statin treatment, 37% did not exhibit any detectable cardiovascular pathology, but 5% had somatic AE (3).

Rhabdomyolisis is the most severe AE of statin treatment, but also the less frequent. An increase in creatine phosphokinase (CPK), up to 10 times higher than normal, has been reported. Less severe AE, such as myalgia and increased hepatic transaminases levels comprise about two thirds of AE reported in this study, but these symptoms receded after discontinuation of the treatment (3).

According to Hioriuchi et al. (10), statins seem to potentially stimulate bone formation in vitro. Statin treatment, in combination with traditional drugs for osteoporosis treatment, such as 17-estradiol, increases bone formation in the jaw, especially in the alveolar bone. This suggests amelioration of periodontal disease in osteoporosis patients, concurrent with decreased breakdown (10).

The frequency and severity of AE due to statin treatment is related to their own potency. Atorvastatin is the most potent (per mg of active principle), therefore the most typically associated with unwanted AE. Fluvastatine exhibits the lowest efficacy, which correlates with less AE. Simvastatin, pravastatin and lovastatin pose intermediate risk of AE.

Our work at the Odontology Service of Primary Attention of Basic Health Area (BHA) Sant Roc (Badalona) has revealed different oral AE, based on spontaneous accounts by most of the patients complaining about discomfort and malcontent. Reported AE include dry mouth and throat (sometimes accompanied by cough), and a constant need for water; bitterness, parestesia, tongue itchiness (tip and/or sides) and the vestibular portion of the lips; insomnia.

Working hypothesis

Hypolipemia treatment with statins could be the cause of diverse oral pathologies.

Aims

General aim: To evaluate if statin uptake causes side effects in the oral cavity.

Specific aims: 1) to describe and quantify the traits of such adverse effects; 2) to evaluate its evolution after discontinuation of the treatment.

Material and Methods

We performed a preliminary observational study of patients from the BHA Sant Roc (Badalona). Inclusion criteria were: patients aged 50-70, diagnosed with hypercholesterolemia (cholesterol over 200 mg/dl), undergoing treatment with statins. Exclusion criteria were: patients diagnosed with Sjögren syndrome, or following treatment with drugs producing dry mouth as side effect (e.g. drugs with anticholinergic activity, benzodiazepines, and diuretics; patients diagnosed with chronic obstructive pulmonary disease or chronic bronchitis). In agreement with these criteria, 28 patients were included in the study. Two of them presented severe cough, itchiness and dryness, and declined further participation; thus, 26 patients completed the study.

Patients were recruited randomly at the Primary Care Centre offices of the BHA for a month. The patients were first informed of the purpose of the study, and upon compliance with the inclusion criteria, they were transferred to the dentist office for revision and further participation in the study.

Each participant was examined twice. Personal and clinical data were collected during the first visit. Anamnesis was directed to the discomfort in the oral cavity: dryness, itchiness/parestesia, bitterness and cough; the patients were questioned about insomnia and other symptoms on their own account. Laboratory tests were conducted, including a basic health revision, liver blood markers, lipid levels, CPK, alkaline phosphatases and bilirubine. Statin treatment was then discontinued for two weeks; this time was selected to grant metabolic elimination of the drug and allow the onset of changes related to the interruption of the treatment.

We then monitored the patient's response in the second visit. These responses were graded according to an improvement index (II), defined as an observable decrease of any symptom; and a recovery index (RI), defined as the absence of each and every symptom.

Results of the study

The distribution of AE observed in our study was: dry mouth (23 patients), itchiness/parestesia in tongue, lips and throat (15 patients), bitterness (14 patients), cough (12 patients) and insomnia (related to previous symptoms).

The distribution by type of statin administered was: simvastatin (n=15), pravastatin (n=7), atorvastatin (n=3), and lovastatin (n=1).

Among the 23 patients presenting dryness, 17 showed improvement over the course of the study (Improvement Index [II]=73.91%). Regarding bitterness, 13 patients out of 14 reported complete remission (Recovery Index [RI]=92.86%). 11 of 12 patients presenting cough improved after discontinuation of the treatment (II=91.67%). Finally, out of 15 patients showing itchiness in tongue, lips and throat, 7 suffering from tongue itchiness exhibited

Table 1. Oral symptoms and evolution after interruption of the treatment with statins.

		First visit	Second visit		
SYMPTOM	Total		No change	II	RI
Dryness	26	23 (88.5%)	6 (26.1%)	17 (73.9%)	0 (0%)
Itch	26	15 (57.7%)	2 (13.3%)	6 ((40.0%)	7 (46.7%)
Bitterness	26	14 (53.8%)	1 (7.1%)	0 (0%)	13 (92.8%)
Cough	26	12 (46.1%)	1 (8.3%)	11 (91.7%)	0 (0%)

total remission (RI=46.67%) and 3 more improved significantly. Another 3 patients suffering from throat itchiness also improved (II=40%) (Table 1).
16 out of 17 patients presenting insomnia improved after interruption of the treatment (II=94.12%).
Regarding the analytical AE, CPK levels were normal; only 2 patients presented a slight increase, but they never were over tenfold the normal levels.

Discussion

In this study, we have observed a high percentage of oral symptoms in patients undergoing treatment with statins; to our knowledge, this is the first report of such adverse effects despite the numerous papers addressing the various side effects of this type of treatment.
On the other hand, we have observed that the AE disappeared in a high percentage of patients after suspension of the treatment, and improvement was observed as early as the third day after interruption.
Dryness improved or remitted in 73.9% of the patients; this is a high percentage considering the average age of the patients and the fact that some of them presented pathologies that induce xerostomy. Similar results were observed regarding cough (91.7%); after dryness improved, nocturnal cough episodes also improved.
Bitterness (92.8%) and itchiness in tongue and lips (86.7%) improved or disappeared in all patients exhibiting those symptoms.
94 % of patients with insomnia reported better rest after interruption of the treatment. When the treatment was resumed, administration was shifted to the morning time despite the pharmacokinetic characteristics of the drugs. This change resulted in improvement of the symptoms and hours of sleep.
In summary, this study reveals a frequent association between oral symptoms and treatment with statins. The fact that there is an important improvement after interruption of the treatment suggests that these symptoms could be a side effect to the treatment. However, these results must be considered carefully, and further studies including more patients are necessary to establish their reliability. This will require the joint collaboration of dentists to determine the AE of statins related to the oral cavity and PCPs to consider alternatives treatment for patients with high risk of cardiovascular disease when the adverse effects are too severe.

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