Statins. A Review on Structural Perspectives, Adverse Reactions and Relations with Non-melanoma Skin Cancer

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The present paper aims to review an important class of medicine widely used in the therapy of hypercholesterolemia, namely statins. We have presented the main adverse reactions and the relation between statins and non-melanoma skin cancer, which we consider to be a novel element in the area of possible adverse reactions.

Keywords: hypercholesterolemia, statins, non-melanoma skin cancer

Action Mechanism

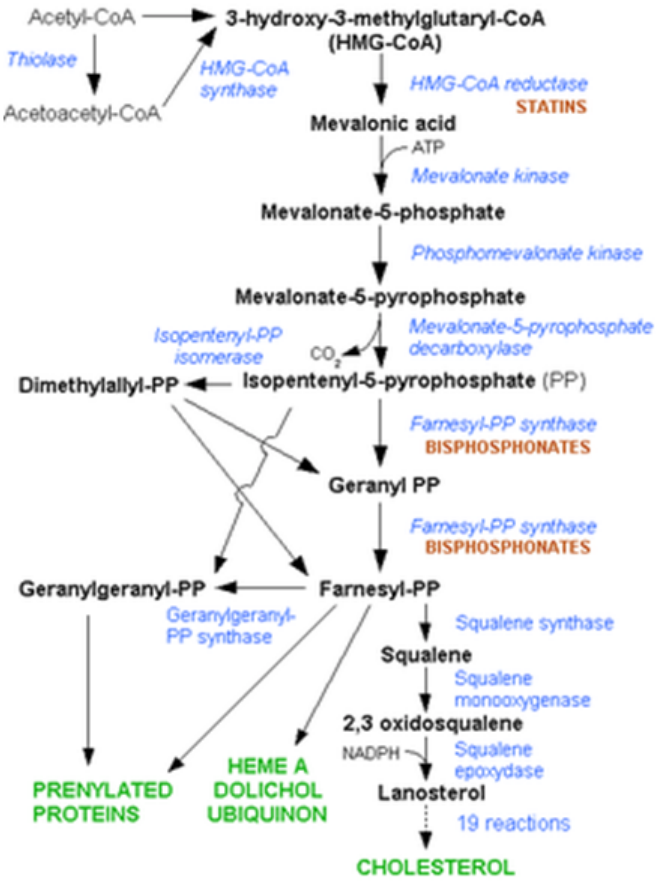
Statins reduce the synthesis of cholesterol in liver, competitively inhibiting the activity of HMG-CoA reductase.

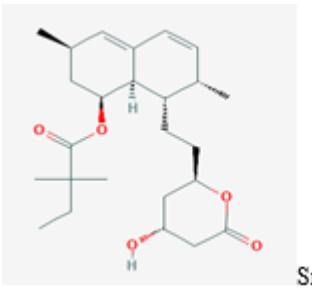
The reduction of intracellular concentration of cholesterol induces an increased expression of LDRD at the surface of the hepatocytes, which results in the high consumption of LDL-C in blood and determines the plasmatic reduction of the concentration of LDL-C and other lipoproteins which contain apo-B, including particles rich in TG.

The degree of reduction of LDL-C depends on dosage and varies from one statin to another. [1, 2]

Statins also decrease the values of triglycerides and increase HDL-C, but these effects are less intense than those on LDL-C. They also have pleiotropic action: they lower oxidative stress and reduce inflammation, thus increasing the stability of atherosclerotic plaque [3]. Lovastatin and simvastatin are inactive prodrugs, activated following hydroxylation in the gastrointestinal tract. Atorvastatin, fluvastatin and rosuvastatin are active as such. After oral administering, statins are absorbed in a percentage of 40 to 75, except for fluvastatin, which is almost completely absorbed. The statin excretion is mainly biliary. They have short halftime (1-3 h), except for atorvastatin (14 h) and rosuvastatin (19 h) [3].

Statin [2]	Commercial name	Derivation
Atorvastatin	Torvast, Totalip	Synthetic
Cerivastatin	LipoBay (Bayer) – withdrawn from the market	Synthetic
Fluvastatin	Lescol, Lipaxan, Primesin	Synthetic
Lovastatin	Lovinacor, Rextat, Tavacor	Natural
Mevastatin	not present in Italy	Natural
Pitavastatin	not present in Italy	Synthetic
Pravastatin	Aplactin, Prasterol, Pravaselect, Sanaprav, Selectin	Natural
Rosuvastatin	Crestor, Provisacor, Simestat	Synthetic
Simvastatin	Liponorm, Medipo, Sinvacor, Sivastin, Zocor, Simbatrix	Natural





Simvastatin

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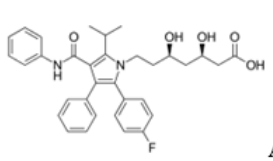
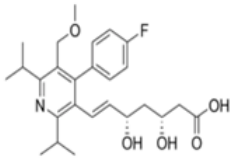
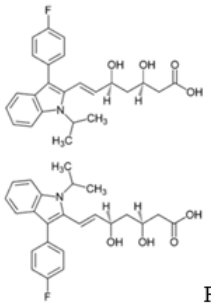
All authors have had an equal contribution to this work



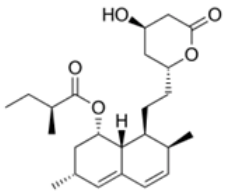
Atorvastatin



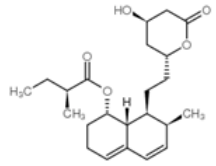
Cerivastatin



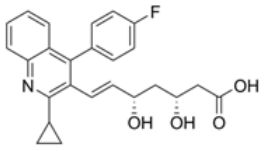
Fluvastatin



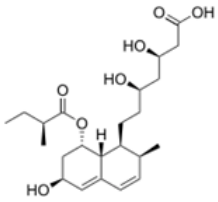
Lovastatin



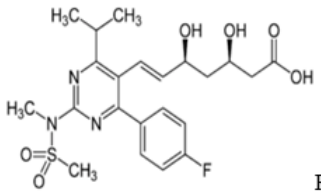
Mevastatin



Pitavastatin



Pravastatin



Rosuvastatin

Adverse reactions of statins

Statins differ in absorption, bioavailability, and adherence to plasmatic proteins, excretion and solubility. Lovastatin and simvastatin are prodrugs, while the other statins are administered in their active form. The absorption rate ranges from 20 to 98%. Many statins are subject to strong hepatic metabolization through the isoenzymes of P450 cytochrome, except for pravastatin, rosuvastatin and pitavastatin. These enzymes are especially expressed in liver and in the wall of the small intestine. Although statins are generally well tolerated, there are some adverse effects which should be considered when prescribed. Statins are safe medicine, but, as any other therapy, adverse reactions do exist. Generally speaking, statins are well tolerated, but various adverse effects are associated: muscular affections, sugar diabetes [4, 5] or cognitive disorders. In clinical studies, such effects occur only rarely, which makes it difficult to establish the causal relation to statins. These effects, whether caused by or only associated to statins, determine the use of lower dosage or the cessation of treatment. They are, in many cases, determining for low adherence to treatment [6].

The mechanisms of the adverse reactions of statins are based on the same isoprenoid intermediaries formed of mevalonic acid as the ones involved in pleiotropic effects. Therefore, these intermediaries of mevalonate pathway, which have, for the most part, beneficial effects, can also have negative consequences [7]. Just as other common drugs, they may also produce recently reported adverse reactions, whose management, corroborated with possible comorbidities, can be problematic [8-16].

Interactions

A large number of medication interaction with statins which may increase the risk of adverse reactions have been described. All statins available at this moment, except for pravastatin, rosuvastatin and pitavastatin are subject to a strong hepatic metabolism through CYP. These isoenzymes are primarily present in liver and intestine. Pravastatin does not go through CYP metabolization, but is metabolized through sulfation and conjugation. CYP3A isoenzymes are the most abounding, but also isoenzymes, such as CYP2C8, CYP2C9, CYP2C19 and CYP2D6, are also involved in statin metabolism. Thus, other pharmacological layers of these CYPs may interfere in the statins metabolism. Therefore, statin therapy may interfere with the catabolism of other drugs metabolized by the same enzymatic system.

The combinations of statins and fibrates may increase the risk of myopathy. The highest risk is for gemfibrozil, and the association of the two drugs should be avoided. The increased risk of myopathy at the combination of statins with other fibrates, such as fenofibrate, bezafibrate and ciprofibrate, seems to be a low one. The increased risk of myopathy in combination with nicotinic acid has been debated, but, in recent assessments, no increased

risk of myopathy has been identified in the case of this agent.

People who take statins must also pay attention to their alimentation during treatment. It is advisable that saturated fat foods, fried food, pork, alcoholic beverages and pastry products be avoided. Grapefruit juice is to be avoided, as it leads to an increase of medicine concentration in blood, which favors the occurrence of adverse reactions. It is advisable that people respect the 5-meal a day rule (3 main meals and 2 snacks), at least one made up of raw salads, boiled or raw vegetables [17, 18].

Statin administration may also have a butterfly effect for some patients, inducing photosensitivity or phototoxicity reactions [19]. Drug-induced photosensitivity refers to the development of cutaneous disease as a result of the combined effects of a chemical and light [20]. Exposure to either the chemical or the light alone is not sufficient to induce the disease; however, when photoactivation of the chemical occurs, one or more cutaneous manifestations may arise.

1. One study reports the results of an investigation of the phototoxicity mechanism induced by pitavastatin and its photoproducts, namely 6-cyclopropyl-10-fluoro-7,8 dihydrobenzo[k]phenanthridine (PP3) and 6-cyclopropyl-10-fluorobenzo[k]phenanthridine (PP4). Phototoxicity was tested in human keratinocytes cell lines NCTC-2544, and the results proved that under the same conditions, all three compounds exhibited phototoxic effects in the model tested. The reduction in cell viability was found to be both concentration- and UVA dose-dependent. (1) Pitavastatin and PP4 induced cell lipid membrane peroxidation along with a significant oxidation of proteins, suggesting that pitavastatin and PP4 exert their phototoxic effect mainly in the cellular membranes. The phototoxicity of pitavastatin may be mediated by the formation of benzophenanthridine-like photoproducts that appear to have high potential as photosensitizers [21]. A special care should be provided when a suspicion of autoimmune disease or a multiple autoimmune syndrome including Lupus erythematous exists [22].

2. Fluvastatin, a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor underwent rapid photodegradation upon Ultraviolet-A (UVA) irradiation. (2) An increase of intracellular calcium followed by an extensive cell lipid membrane peroxidation and a significant oxidation of model proteins were induced by fluvastatin and its photoproduct, suggesting that these compounds exerted their toxic effect mainly in the cellular membranes. On the basis of our results, the phototoxicity of fluvastatin may be mediated by the formation of benzocarbazole-like photoproduct that acts as strong photosensitizer. (2) Due to pharmaco-toxic effects, secondary Staphylococcal or other infections can occur on the skin or on other organ [23-25].

3. Rosuvastatin contains a 2-vinylbiphenyl-like moiety and has been previously described to decompose under solar irradiation, yielding stable dihydrophenanthrene analogues- rosuvastatin main photoproduct (ppRSV) [26]. Laser flash photolysis studies revealed a triplet-triplet energy transfer from the triplet excited state of ppRSV to thymidine, leading to the formation of cyclobutane thymidine dimers, an important type of DNA lesion. Rosuvastatin, through its major photoproduct ppRSV, should be considered as a potential sensitizer [26].

4. Chronic actinic dermatitis occurs secondary to simvastatin [27, 28].

5. Another study showed that statin use can reduce the risk of diffuse large B-cell lymphomas and plasma cell lymphomas, but not other non-Hodgkin lymphomas [29] but a clear duration- or dose-response relationships were observed [29].

6. It might be necessary to mention to our patients before starting the treatment, the possiblity that statins, as other drugs like tetracicline [30] and hidrochlorotiazide [31] to be included in the black list of the purported to be carcinogenic drugs.

7. Statins also have immunomodulatory properties including increasing regulatory T cells, which may lead to an increased risk for non-melanoma skin cancer NMSC [32-36].

8. Statins have been associated with increased photosensitivity, which may be due to their effect on signal-transduction pathways leading to proinflammatory cytokines [37].

9. The literature has also reported photosensitivity and cutaneous side effects associated with statins, which may be related to increased NMSC risk, although the mechanisms are also not well understood [38, 39].

10. Statins (atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin) generate phototoxic reactions, photoallergic reactions, a planus lichenoides reaction and pseudo porphyria [40].

Phototoxic reactions result from direct damage to tissue caused by a photoactivated compound. Many compounds have the potential to cause phototoxicity [37]. Most have at least one resonating double bond or an aromatic ring that can absorb radiant energy. Most compounds are activated by wavelengths within the UV-A (320-400 nm) range, although some compounds have a peak absorption within the UV-B or visible range.

In most instances, the photoactivation of a compound results in the excitation of electrons from the stable singlet state to an excited triplet state. As excited-state electrons return to a more stable configuration, they transfer their energy to oxygen, leading to the formation of reactive oxygen intermediates. Reactive oxygen intermediates such as an oxygen singlet, superoxide anion, and hydrogen peroxide damage cell membranes and DNA. Signal transduction pathways that lead to the production of proinflammatory cytokines and arachidonic acid metabolites are also activated. The result is an inflammatory response that has the clinical appearance of an exaggerated sunburn reaction. Photoallergic reactions are cell-mediated immune responses in which antigen is a light-activated drug [37]. Photoactivation results in the development of a metabolite that can bind to protein carriers in the skin to form a complete antigen. The reaction then proceeds exactly as other cell-mediated immune responses do. Specifically, Langerhans cells and other antigen-presenting cells take up the antigen and then migrate to regional lymph nodes. In those locations, the Langerhans cells present the photoallergen to T lymphocytes that express antigen-specific receptors. The T cells become activated and proliferate, and they return to the site of photoallergen deposition. In the skin, the T cells orchestrate an inflammatory response that usually has an eczematous morphology if the photoallergen is applied topically or the characteristics of a drug eruption if administered systemically. Photosensitivity/phototoxicity has implications on the hydro lipid barrier at the skin level, especially on the facial areas, the use of such drugs may have implications for the evolution of photosensitive dermatoses such as Rosacea, or factors involved in its development such as Demodex Folliculorm or its endosymbions belonging to the cutaneous microbioma [38-46].

The risk of neoplasia under treatment with this class of medicine is mentioned in a few reviews, without being supported by clear evidence [18]. On the contrary, some preclinical studies or in-vitro survey have shown that lipophilic statins (e.g. simvastatin) in neoplasias appear to have anti-proliferative and proapoptotic, therefore anticancer properties[47-50].

Recent papers suggested: *Agents that modulate sterol levels might influence the Hedgehog signalling (Hh) pathway*. The Hh pathway plays a key role in directing growth and patterning during embryonic development. Hh signalling leads to the development of BCCs. Thus, sterols may be a new therapeutic target for the treatment of BCCs, and readily available agents such as statins (HMG-CoA reductase inhibitors) or vitamin D might be helpful in reducing BCC incidence [51].

Other papers suggested that among a large cohort of individuals (12,123 patients) with BCC, statin therapy was not significantly associated with risk of subsequent BCC [52].

The most recent article about the statins and skin cancer concluded that history of high cholesterol level was not associated with skin cancer risk. Longer duration of statin use was associated with a trend toward higher BCC risk in men than in women [53].

The authors have produced an interesting work, with impressive data [53] and we have some questions that we would like them to address. Might the observed difference in effect of statin use on risk of basal cell carcinoma (BCC) between men and women be attributable to evidence to the effect that statins are, in themselves, less effective in women [54].

BCC is, by itself, more common in men. Could this have also skewed their data towards preponderance of BCC in men in their study group? Would the authors care to comment?

There is also a higher citrus consumption amongst men in this study [53]. Perhaps the authors could further stratify for us the difference in orange and grapefruit consumption of their population. Grapefruit juice is known to increase statin levels via hepatic enzyme inhibition, which might contribute to increased risk of BCC. This information could be valuable in the care of our patients on statins, especially those disposed to try healthier lifestyles that may include significant citrus juice consumption. Possible confounding factors not discussed by the authors include medications such as hydrochlorothiazide and tetracycline, both commonly administered drugs, which are also associated with skin cancer risk [54, 55]. Could the authors kindly review their data and confirm usage/non-usage of this medication? This might raise the question of their impact on cancer risk for the populations they studied.

Statins and hydrochlorothiazides can be prescribed together for cardiovascular disease. Both are known photosensitisers [55, 56] and a synergistic effect of combining these medications may exist. Could the authors kindly review their data and let us know if such associations exist? If so, then a very interesting question would be why the incidence of skin cancer was not significant in their population with such combined medication, whereas it was when analysed separately [57]. We might discover that, counterintuitively, this combination is not synergistic and could even be the opposite. It is also worthwhile to discuss the role of action in a carcinogenic sense, especially on the field of some patients, or in areas interpreted as locus minoris resistentiae, Wolf isotopic response or Koebner type 5 phenomenon by some authors in recent articles [58, 59].

A valuable lesson on the actions of these medications could be learnt from this analysis of the authors data. Could carvedilol, possessing potential anticancer effects via nuclear signalling and antioxidant action replace hydrochlorothiazide in combination with statins as an alternative? The data collected by the authors is highly impressive. Yet it is data on a very educated group, possessing medical knowledge, whose lifestyle (including vegetable and fruit consumption, as well as exercise, potential protective factors against skin cancer) might impact statin use (frequency and dosage) and even cancer risk. This might have skewed their data self-correcting in a larger population. Do they feel that their data can, nonetheless be generalized to the wider population? Their answer would certainly be helpful in determining our approach and that of colleagues in other specialties who might encounter patients on long-term statin therapy.

Aside from informing patients of skin cancer risk with statins, do the authors feel that warnings would be needed on drug labels and patient information leaflets as has been mooted elsewhere?

With consideration to medical ethics, it is useful, under these circumstances, before the prescription and administration of medicine of the statin class, to warn our patients against the possible adverse reactions which may occur, by making them sign the informed consent form [60, 61]. In the future, for such possible risks to be avoided, new substances - perhaps plant extracts of limited adverse reaction potential - and non-aggressive alternative treatments should be investigated and used [62, 63], bearing in mind that knowledge removes discomfort [64, 65].

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