УДК 615.27+615.015.26.001

Statin intolerance: the clinician's perspective *

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KEY WORDS: statin, statin intolerance, muscle side effects, myalgia, low-dose statin therapy

Introduction

Statins effectively decrease cardiovascular risk, and cholesterol lowering with statins has become a cornerstone of cardiovascular disease prevention for a wide range of patients [2]. Despite this, adequate use of statins is limited by adverse symptoms in many patients [6, 18, 30], which leads to statin discontinuation in some patients, and low adherence to therapy in others. The issue of statin intolerance is, therefore, of great clinical importance.

Despite the existence of statin intolerance having been widely acknowledged, a large degree of variability remains as to what is considered to be statin intolerance. In addition, there is significant uncertainty regarding the actual incidence, and there is insufficient knowledge concerning the best therapeutic approaches to the problem. Most cases of statin intolerance are related to muscle complaints [8, 11, 24], with increased liver or muscle enzymes [4], various neurological symptoms [23] and other problems being much less frequent. The glycemic effects of statins are occasionally included as a symptom of statin intolerance; although, they are rather undesired side effect rather than serious finding necessitating discontinuation of the therapy in the individual cases. Moreover, as we have previously discussed elsewhere [28], the diabetogenic effects of statins are generally overestimated.

It should be noted that all of the mentioned symptoms can stem from a number of different causes and are often unrelated to actual statin use. However, even among patients with true statin-related symptoms, many can tolerate lower doses of the same statin, or perhaps a different statin. Establishing a diagnosis of statin intolerance is therefore less straightforward than it might appear, and an adequate therapeutic approach is more complex than simple discontinuation of statin therapy.

As a result of these complexities, statin intolerance is currently gaining increased attention and several guidelines [11, 16, 27] and review papers [17, 19, 20] have recently been published, thereby providing an in-depth discussion of this complicated, and often controversial, topic. Practicing physicians, however, may find the aforementioned recommendations somewhat lengthy and difficult to implement in their daily practice. In this review, we propose a practical definition of statin intolerance and outline a therapeutic approach to patients with this condition.

Definition of statin intolerance

In general terms, statin intolerance can be defined as the occurrence of: 1) adverse symptoms perceived by the patient to be unacceptable, and/or 2) laboratory abnormalities suggesting undue risk, which are attributed to statin therapy and lead to its

* Current Atherosclerosis Reports.– 2015.– Vol.17 (12).– P. 69 (Передрук з дозволу ScreenPro FH).

On behalf of ScreenPro FH Project: M.V. Ezhov (Russia), Z. Fras (Slovenia), T. Freiberger (Czech Republic), D. Gaita (Romania), A. Goudev (Bulgaria), M. Kayikcioglu (Turkey), G. Latkovskis (Latvia), E.M. Mirrakhimov (Kyrgyzstan), E. Mitchenko (Ukraine), G. Paragh (Hungary), Z. Petrulioniene (Latvia), B. Pojskic (Bosnia and Herzegovina), K. Raslova (Slovakia), Z. Reiner (Croatia), A. Rynkiewicz (Poland), A.V. Susekov (Russia), N. Tasic (Serbia), A. Tselepis (Greece).

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discontinuation. For practical purposes, descriptions regarding acceptability of symptoms, attributability to statin therapy, and the degree of intolerance, need to be better defined.

Most cases of statin intolerance are related to patient complaints; the discontinuation of therapy due to laboratory abnormalities is far less common. Thus, in most cases, decisions pertaining to statin intolerance is the patient's decisions. In this context, it is important to note that some degree of adverse symptoms might be tolerated by the patient and does not necessarily imply intolerance of therapy. Statin intolerance is not simply the occurrence of symptoms in general, but rather those symptoms that are perceived to be unacceptable. Hence, the patient's subjective assessment of perceived risks and inconveniences, versus the benefits of therapy, are at the core of an effective approach to the issue of statin intolerance.

When experienced during the course of statin therapy, myalgia and other adverse symptoms are often unrelated to treatment, and most patients with a history involving episodes of these symptoms are able to tolerate adequate statin therapy [15, 31]. Identifying true cases of statin intolerance is, therefore, of great practical importance to avoid unnecessary discontinuation of statins from patients who would otherwise benefit from them. However, evaluating the likelihood that the adverse symptoms are causally related to statins is often a difficult task. Close temporal association to statin therapy is an important feature that suggests causality. Symptoms are more likely to be attributable to statins if they appear within the first month of statin therapy, improve upon discontinuation, and reoccur after readministration [6, 18]. Consequently, dechallenge-rechallenge testing is an important evaluation tool when assessing statin intolerance. Similarly, it is important to rule out conditions that are associated with symptoms that mimic statin intolerance (musculoskeletal disorders, in particular), as well as contributing factors that may precipitate symptom manifestation, such as hypothyroidism [22], vitamin D deficiency [10] or drug interactions.

Given the specifications mentioned above, we propose the following **definition of statin intolerance for use in clinical practice:**

Statin intolerance is the occurrence of 1) adverse symptoms perceived by the patient to be unacceptable, and/or 2) laboratory abnormalities suggesting undue risk, which are attributed to statin therapy and lead to its discontinuation.

To be attributed to statins:

- symptoms or abnormalities should be temporally associated with the initiation of statin therapy, improve upon discontinuation, and reoccur after the re-administration of therapy, and
- known precipitating factors and conditions with similar presentations should first be excluded. These primarily include musculoskeletal diseases, hypothyroidism, vitamin D deficiency, strenuous exercise, intercurrent illness or drug interactions (e.g. azole antifungals, macrolide antibiotics, verapamil).
- Mild symptoms should not be considered intolerance, provided they are deemed acceptable by the patient.
- Among patients presenting with statin intolerance, there is great variability regarding the number and doses of statins they are unable to tolerate. Some patients are intolerant of virtually all statins, even in low doses; others only experience adverse symptoms with a particular statin, or only with the highest doses of particular statins. With this in mind, we propose two degrees of statin intolerance for consideration:
- complete statin intolerance: the inability to tolerate a minimum of three statins at their usual lowest daily starting doses, and
- partial statin intolerance: the inability to tolerate statin therapy in the form and dosages required to achieve treatment goals (including the highest doses of potent statins, if needed).

For the purposes of this definition, the lowest daily starting doses of statins are proposed as rosuvastatin 5 mg, atorvastatin 10 mg, simvastatin 20 mg, lovastatin 20 mg, pravastatin 40 mg, fluvastatin 40 mg, and pitavastatin 2 mg.

Partial intolerance is pragmatically defined with respect to the therapeutic needs of individual patients. Inability to tolerate some statins, or some doses, should not be considered as statin intolerance, provided it does not interfere with the achievement of treatment goals.

Therapeutic approach to statin intolerance

Most patients who experience adverse symptoms when using statins are able to tolerate at least one statin, albeit sometimes only when administered in an altered dosing regimen. Given the profound cardiovascular benefits of statins, statin therapy remains the mainstay of lipid-lowering treatment for most of these patients.

In many patients, adverse symptoms are unrelated to statin usage, especially in those with atypical and intermittent presentations following long periods of treatment. The first step in approaching patients who experience adverse symptoms during the course of statin therapy is therefore to assess whether the symptoms are likely attributable to statins. This includes obtaining a complete history of symptoms, temporary withdrawal of statins followed by and rechallenge, as well as seeking other causes of the symptoms [11]. If statin intolerance appears unlikely, the patient can probably tolerate adequate therapy with the same, or alternative, statin.

Likewise, potential provoking factors such as hypothyroidism, vitamin D deficiency, or drug interactions should also be evaluated, as correcting these problems may improve statin therapy tolerance.

In patients with statin intolerance, very low doses of statins administered via an altered dosing regimen should be attempted and, if tolerated, should be gradually increased to achieve the highest tolerable doses. With this cautious approach, the majority of patients are able to tolerate at least some degree of statin therapy. In addition, other lipid-lowering drugs may be needed to achieve the appropriate targets. The principles of lipid-lowering therapy in cases of statin intolerance are discussed in the following sections.

Lifestyle interventions reduce blood cholesterol levels and improve other cardiovascular risk factors, but adherence to these measures is low among the general patient population. Encouraging and motivating patients to improve adherence to lifestyle measures may aid in the attainment of treatment goals in cases where the possibility of using lipid-lowering drugs is limited.

The ultimate goal of lipid-lowering treatment is to decrease cardiovascular risk, which depends upon the interplay of multiple risk factors. Control of other risk factors – especially those of hypertension and smoking – effectively reduces cardiovascular risk, which may move the patient to a lower-risk category with less stringent, and more easily attainable, lipid goals.

Coenzyme Q10 (CoQ10) supplementation is frequently used for statin myalgia, but the evidence in support of its use has, thus far, been contradictory. Recently, a well-designed trial [29], in conjunction with a meta-analysis of previous smaller trials [3], consistently failed to demonstrate a difference between CoQ10 and placebo, demonstrating that beneficial effect of CoQ10 supplementation in patients with statin-induced myalgia is quite unlikely.

Statin therapy

In patients with partial statin intolerance (i.e. those who require, but are unable to tolerate, moderate or high doses of potent statins), lower doses, or less potent statins, should be used.

For patients unable to tolerate any statin at the usual starting daily dose, there is emerging agreement that very low doses, and/or less-than-daily dosing, should be attempted [8, 19]. Since the association between statin dose and LDL-C is logarithmic, reducing the usual dose of a statin to one-half (or even to one-quarter) still provides a reasonable degree of lipid lowering (ultimately, this approach is simply applying the notorius «rule of six» in the reverse direction). Multiple studies of patients with previous statin intolerance have demonstrated that rosuvastatin administered once or twice weekly (at a mean dose of 10 mg per week) produced an LDL-C reduction of 23–29 %, and was well tolerated by 74–80 % [1, 9, 25] of patients. In a recent review report from a specialized lipid clinic, 90 % of patients referred for intolerance to multiple statins were actually able to tolerate statin therapy, although the majority were at reduced dose and less-than-daily dosing [12]. Obviously, the efficacy of non-licensed dosing regimens in terms of reducing cardiovascular risk has not been studied. On the other hand, most statin effects are mediated through the lowering of LDL-C; therefore, it would seem reasonable to assume that the cardiovascular risk reduction achieved with alternate statin dosing regimens would be proportionate to their LDL-lowering effects.

In terms of a practical approach to statin intolerance, listening to the patient's complaints and fears is crucial to encourage greater receptivity and willingness to try various statins and dosing schedules, some of which may be associated with adverse symptoms [11, 12]. These patients need to understand that i) while these symptoms may be bothersome, they are rarely dangerous, and ii) they are free to discontinue the drug at any time. It is equally important that physicians emphatically explain the beneficial effects of therapy in terms of cardiovascular event reduction.

In order to prevent unnecessarily intense symptoms of statin intolerance and improve patient adherence to statin therapy in the general popula-

tion, it may be wise to initiate statin therapy in statin-naive patients with low or moderate (rather than high) doses in the majority of cases. Patients who previously tolerated lower doses are much more willing to return to them in cases where they experienced problems with higher doses, compared to those who were intolerant to a higher starting dose. It is also advisable to perform both creatine kinase and liver tests prior to commencing statin therapy in order to establish reference baseline values in case the patient develops elevations in these tests during therapy.

Non-statin lipid-lowering drugs

Other lipid-lowering drugs may be needed to achieve appropriate targets, either in combination with statins, or alone, if statins are not tolerated at all. A combination of these drugs and low-dose statin therapy can provide reductions in LDL-C similar to those obtained with high doses of statins.

Ezetimibe decreases LDL-C by 15–20 % (either in combination with statins or as monotherapy) and is widely used in patients with statin intolerance. Ezetimibe is well tolerated, but the evidence of cardiovascular benefit is limited to one trial that demonstrated a modest 6 % reduction of cardiovascular events [7].

Fibrates are primarily used to lower triglycerides and increase HDL-C; they also decrease LDL-C levels, but to a lesser extent. The effect on LDL-C is more pronounced in patients with hypertriglyceridemia. Accordingly, the reduction of cardiovascular risk with fibrates is only 10 % in unselected patient population, but is substantially greater (≈ 30 %) in patients with hypertriglyceridemia [13]. As such, fibrates represent a reasonable option in these patients. However, caution must be exercised when combining fibrates with statins, as the combination may increase the risk of myalgia.

Bile acid sequestrants (resins) provide LDL-C reduction that is comparable to that observed with ezetimibe, and they have been proven to reduce cardiovascular events. Resins are safe, but poorly tolerated, due to gastrointestinal side effects. The recently-developed colesevelam has fewer side effects and better patient compliance.

Niacin is similar to fibrates relative to its effect on blood lipids, but its use in clinical practice has dropped substantially after two clinical-endpoint trials failed to demonstrate cardiovascular benefits of niacin therapy [5, 14].

PCSK9 inhibitors are a novel class of lipid-lowering drugs; they are in the late stage of development and are expected to become available in the near future. They reduce LDL-C levels by ≈ 50 %. Meta-analyses of phase 2 and 3 trials demonstrated a > 50 % reduction of cardiovascular events with evolocumab and alirocumab [21, 26], and the results of major clinical trials are eagerly awaited by clinicians. Statin intolerance is one of the indications for use of PCSK9 inhibitors that are currently under investigation.

Conclusions

Muscle problems and other adverse symptoms associated with statin use are relatively frequent reasons for non-adherence and discontinuation of statin therapy, which can contribute to adverse cardiovascular outcomes. However, most patients who experience objectionable symptoms during statin use are still able to tolerate at least some degree of statin therapy. The clinician's challenge is therefore to help their patients find their way back to statins.

In essence, this task comprises only a few steps: First, identify patients with unlikely statin intolerance, and who can therefore probably continue some type of adequate statin therapy. A pragmatic definition of statin intolerance, as outlined above, may be useful in this respect. Second, in cases with statin intolerance, consider very low doses of statins and/or altered dosing regimens. In addition, other lipid-lowering drugs may be needed, in conjunction with changes in lifestyle and better control of other cardiovascular risk factors. With this cautious and multifactorial approach, reasonable improvement in blood lipid levels, as well as a marked reduction in global cardiovascular risk score, can be achieved in most patients.

As simple this approach may appear, it may prove difficult in practice. Listening to patients' complaints and fears, explaining the benefits of therapy, and motivating patients to try various therapeutic schedules (some of which may be associated with adverse symptoms) are often difficult and time-consuming tasks. From a clinician's perspective, a successful approach to statin intolerance primarily entails the art of successful communication with the patient.

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Надійшла 14.03.2016 р.

Непереносність статинів: точка зору клініциста

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Біль у м'язах та інші небажані симптоми, пов'язані із застосуванням статинів, – часті причини недотримання призначеної терапії та її відміни, що призводять до невідповідного контролю гіперліпідемії й підвищеного серцево-судинного ризику. Однак більшість пацієнтів, у яких виникають небажані симптоми при лікуванні статинами, можуть переносити терапію щонайменше низькими дозами. Враховуючи значну користь цих препаратів для серцево-судинної системи, можна зробити висновок, що відповідний практичний підхід до непереносності статинів має велике клінічне значення. Непереносність статинів може бути визначена як поява болю у м'язах або інших небажаних симптомів, пов'язаних із терапією статинами, які стають причиною її відміни. Насправді в більшості пацієнтів ці симптоми фактично не пов'язані із застосуванням статинів, особливо в осіб з нетиповими виявами після тривалого лікування. Таким чином, першим кроком у пошуку підходу до ведення пацієнтів з небажаними симптомами протягом курсу лікування статинами є визначення тих хворих, у яких справжня непереносність статинів малоймовірна, оскільки існує ймовірність того, що більшість цих пацієнтів зможуть переносити відповідну терапію статинами. У пацієнтів з непереносністю статинів слід спробувати змінений режим дозування з дуже низькими дозами статинів, і в разі переносності дози необхідно поступово збільшувати її до досягнення найвищої переносної. Окрім цього, при повній непереносності статинів можуть знадобитися інші ліпідознижувальні препарати, або в комбінації зі статинами, або в якості монотерапії. Якщо підтверджено, що в ході терапії важко досягти цільового рівня ліпідів, у цьому випадку суворий контроль інших чинників ризику може допомогти знизити серцево-судинний ризик.

Ключові слова: статини, непереносність статинів, побічні ефекти, біль у м'язах, терапія низькими дозами статинів.

Непереносимость статинов: точка зрения клинициста

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Боль в мышцах и другие нежелательные симптомы, связанные с применением статинов, – частые причины несоблюдения назначенной терапии и ее отмены, приводящие к несоответствующему контролю гиперлипидемии и повышенному сердечно-сосудистому риску. Однако большинство пациентов, у которых возникают нежелательные симптомы при лечении статинами, могут переносить терапию низкими дозами. Учитывая значительную пользу этих препаратов для сердечно-сосудистой системы, можно сделать вывод, что соответствующий практический подход к непереносимости статинов имеет большое клиническое значение. Непереносимость статинов может быть определена как появление боли в мышцах или других нежелательных симптомов, связанных с терапией статинами, которые становятся причиной ее отмены. На самом деле у большинства пациентов эти симптомы практически не связаны с применением статинов, особенно у лиц с нетипичными проявлениями после длительного лечения. Таким образом, первым шагом в поиске подхода к ведению пациентов с нежелательными симптомами в течение курса лечения статинами является определение тех больных, у которых настоящая непереносимость статинов маловероятна, поскольку существует вероятность того, что большинство этих пациентов смогут переносить соответствующую терапию статинами. У пациентов с непереносимостью статинов следует попробовать изменить режим дозирования с очень низкими дозами статинов, и в случае переносимости дозы необходимо постепенно увеличивать ее до достижения наивысшей переносной. Кроме этого, при полной непереносимости статинов могут понадобиться другие липидоснижающие препараты, или в комбинации со статинами, или в качестве монотерапии. Если подтверждено, что в ходе терапии трудно достичь целевого уровня липидов, в этом случае строгий контроль других факторов риска может помочь снизить сердечно-сосудистый риск.

Ключевые слова: статины, непереносимость статинов, побочные эффекты, боль в мышцах, терапия низкими дозами статинов.