

Insights Into Statin Intolerance

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Introduction

A panel of experts convened in Boca Raton, Florida, in July 2014, to discuss issues surrounding statin intolerance. The panel adopted a 3-pronged approach, focusing on aspects of statin intolerance in the laboratory, in the clinic, and in the literature.

Participants included: Dr. JoAnne Foody (moderator): Executive Director, Global Director Scientific Affairs Cardiovascular, Global Center for Scientific Affairs, Merck Research Labs. Dr. Seth Baum: Medical Director, Women's Preventive Cardiology, Boca Raton Regional Hospital, and CMO, MB Clinical Research, Boca Raton, FL. Dr. Michael Koren: CEO, Jacksonville Center for Clinical Research, Jacksonville, Florida. Dr. Stephen Kopecky: Cardiologist, Preventive Cardiology, Mayo Clinic, Rochester, Minnesota. Dr. James McKenney: Professor Emeritus at Virginia Commonwealth University, President and CEO at National Clinical Research, Inc., Richmond, Virginia. Dr. Laurence Sperling: Professor of Medicine (Cardiology) and Director of the Emory Heart Disease Prevention Center; Professor of Global Health, Hubert Department of Global Health, Rollins School of Public Health at Emory University, Atlanta, Georgia. Dr. Nathan Wong: Professor and Director of the Heart Disease Prevention Program at University of California, Irvine, California.

This document represents a synthesis of the roundtable conversation.

In the Laboratory

Q: What laboratory tests help to confirm a diagnosis of statin intolerance?

Dr. Sperling: There is no test that typically confirms a diagnosis of statin intolerance, and this is one of the reasons that it is such a difficult clinical entity to address.

Dr. Wong: Obtaining adequate baseline information on current muscle and other symptoms before a patient begins a statin is important, as symptoms are often erroneously

attributed to the statin when they were actually present beforehand.

Creatine Kinase Levels: Some papers in the literature suggest that measurement of creatine kinase (CK) is most appropriate for a patient workup, after symptoms of intolerance have emerged.

Some physicians prefer to obtain a baseline CK for comfort, whereas others claim that with a baseline CK, you may end up pursuing the enzyme forever.

Changes in CK levels can occur daily, and CK is not a diagnostic tool. Although there is a general tendency not to look at CK levels in the absence of a specific complaint, a CK measurement 1 to 2 days following intense exercise may be appropriate to see what the highest values might be.

Myositis (defined as muscle inflammation) seems to be associated with exercise, and almost without exception with CK elevations; myalgia (defined as muscle pain) can be relatively nondescript and is seldom associated with CK elevation.

Liver Function Testing: Patients are interested in their liver enzymes. It is recommended that alanine aminotransferase (ALT) and aspartate aminotransferase (AST) measurements be done at baseline and then be repeated, but there is little need for ongoing monitoring of liver enzymes unless warranted.

The ALT and AST levels are measured to determine if a patient is developing liver damage, or even liver failure, which may occur idiosyncratically in 1 in a million patients. This is the same incidence that is seen in patients who are not on statins, so a physician might ask what is really being accomplished by obtaining these measurements. It should be noted that ALT and AST will often increase transiently and harmlessly during the first few weeks of statin therapy.

It should also be noted that some patients may be heavy drinkers, and this may confuse the issue with regard to liver function testing.

Lipids and Low-Density Lipoprotein Cholesterol Targets: An initial assessment should include a lipid panel, as this is a marker of both statin adherence and efficacy. If there are issues with not achieving the desired goals, then adherence needs to be examined and addressed. Familial hypercholesterolemia should be considered when statin therapy is less effective than anticipated.

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The National Lipid Association (NLA) has released recommendations for patient-centered treatment of dyslipidemia, which include a low-density lipoprotein cholesterol (LDL-C) goal of <100 mg/dL for patients at low, moderate, and high risk, and an LDL-C goal of <70 mg/dL for patients at very high risk.¹

One of the biggest misunderstandings about the new Guidelines from the American College of Cardiology/American Heart Association (ACC/AHA) is that they specifically recommend not to check lipids. The ACC/AHA Guidelines do make a specific recommendation to measure LDL-C levels regularly after statin initiation for the purposes of checking for therapeutic response and adherence, and to try to get LDL-C levels reduced by $\geq 50\%$ if on a high-intensity statin, or $\geq 30\%$ if on a statin of moderate intensity.

Vitamin D: There appears to be a relationship between low vitamin D levels and myalgia. A statin may be blamed incorrectly for symptoms when simple repletion with vitamin D may resolve the symptoms. For this reason, there may be some value to vitamin D testing as a baseline to proactively resolve myalgia; this could also improve compliance.

There had been questions raised concerning the quality of the vitamin D assay, but they have since been resolved.

Vitamin D levels can be low, even in individuals such as farmers who are outdoors all day long.

The VITamin D and Omega-3 Trial (VITAL) is ongoing and should answer some questions about vitamin D in regard to cardiovascular health, though it will not answer questions related to statin intolerance. There are costs involved in measuring vitamin D levels, and there needs to be some value in these tests.

Coenzyme Q10: Measurement of coenzyme Q10 (CoQ10) appears in some algorithms, but there are limited data available, as well as a lack of US Food and Drug Administration (FDA) oversight for this supplement.

There have been trials with CoQ10 supplementation, but the evidence of benefit is conflicting. CoQ10 is generally very well tolerated, with the exception of occasional restlessness when taken at night.

Q: Is there any interaction between statins and the natural decline of strength with aging?

In older patients, there is a natural decline in strength and agility, and concurrently, they are receiving statins; however, these patients are also at greatest risk for a heart attack.

The side-effect profile in this older population will be different, however, as younger patients may tend to complain more about cognitive dysfunction; this is because they remain active in the workforce and can be very sensitive to their level of performance. Older patients are more prone to complaints of generalized aches and pains that are, for the most part, easier to manage.

Once they are beyond the age of 75 years, patients should be on statins to reduce the chances of myocardial infarction.²

Dr. Sperling: The high prevalence of myopathies and myalgia is overemphasized, as most patients do not experience these symptoms. The message is not that 10% of patients experience these symptoms, but that 90% do not. Patients need to understand the typically favorable benefit-to-risk ratio, and as a whole, the messages for patients and physicians should focus on the positive.

Q: What effects do acute physical activities have on muscle complaints associated with statin use?

Following exercise, elevations in CK levels always seem to resolve quickly; but at the same time, it is prudent to see what the highest elevations look like, as there can be a great deal of variability with exercise.

As the older population becomes more active, it can become more difficult to advise them.

Both before and after a big run, or other strenuous activity, it may be appropriate for patients to withhold their statin for several days.

Under most circumstances, there are no measurable negative effects from statin withdrawal in the short term. The risks emerge over the long term, and for an at-risk patient to be deprived of statin therapy, this can come with significant effects.

Q: Are there patients in whom statin-induced myalgia may be cumulative, and perhaps even irreversible?

Statin use may hasten the muscle decline associated with aging, but this is believed to be reversible in the vast majority of instances, as muscles can train at any age.

In the rare circumstance of necrotizing autoimmune myositis (NAM), muscle damage can be prolonged or even permanent. This condition results from the inappropriate production of antibodies to the enzyme HMG-CoA reductase.

In the Clinic

Q: What do you do when a patient tells you that they are experiencing muscle pain and associate it with their statin?

It is important to understand that many patients are not taking their statins; physicians may think all of their patients are adherent, but often they are not. Many patients discontinue their statin due to side effects, but they do not have the time or inclination to report this to their health care provider.

Part of the challenge is to identify intolerance when there are vastly different ways patients do, or do not, present with symptoms.

Patients are often misled by things they hear or have read on the Internet. When they initiate statin therapy, they often expect to experience symptoms, and this becomes a self-fulfilling prophecy, which underscores the importance of a baseline assessment of symptoms.

Q: What is your definition of statin intolerance?

Dr. McKenney: According to the FDA, a patient must have been tried on 1 statin, at any dose, and exhibit symptoms, and on a second statin at the lowest dose, and also had symptoms. These criteria seem too onerous, however, and are not consistent with how we think as health care providers. It is difficult to find patients who meet these criteria because statins are simply not prescribed in this way.

Anyone not taking as much statin as they should be taking is at least partially statin intolerant, and most patients may be, to some extent. Some would argue, consistent with the new ACC/AHA Guidelines (Table 1),³ a patient should be taking the maximum tolerated dose, and if they are not, they are at the very least partially statin intolerant.

Table 1. High-, Moderate-, and Low-Intensity Statin Therapies^a

| High Intensity | Moderate Intensity | Low Intensity |
|---|---|--|
| (Daily dose lowers LDL-C, on average, by approximately $\geq 50\%$ ^b) | (Daily dose lowers LDL-C, on average, by approximately 30% to $< 50\%$ ^b) | (Daily dose lowers LDL-C, on average, by approximately $< 30\%$ ^b) |
| Atorvastatin 40–80 mg | Atorvastatin 10 (20) mg | Simvastatin 10 mg |
| Rosuvastatin 20 (40) mg | Rosuvastatin (5) 10 mg | Pravastatin 10–20 mg |
| | Simvastatin 20–40 mg | Lovastatin 20 mg |
| | Pravastatin 40 (80) mg | Fluvastatin 20–40 mg |
| | Lovastatin 40 mg | Pitavastatin 1 mg |
| | Fluvastatin XL 80 mg | |
| | Fluvastatin 40 mg BID | |
| | Pitavastatin 2–4 mg | |

Abbreviations: ACC/AHA, American College of Cardiology/American Heart Association; BID, twice daily; FDA, US Food and Drug Administration; LDL-C, low-density lipoprotein cholesterol; RCT, randomized controlled trial.
Italic font indicates statins and doses approved by the FDA but not tested in the RCTs reviewed by ACC/AHA Guideline authors.
^aAs defined by Stone et al.³ ^bIndividual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice. There might be a biological basis for a less-than-average response.

Many patients referred for statin intolerance have not been rigorously tried on a variety of statin therapies.

Pragmatic Statin Intolerance: There needs to be a clinical definition as opposed to a regulatory definition. Although statin intolerance is not evidence-based, it is the failure to reach evidence-based doses of statins as recommended by the ACC/AHA Guidelines that defines statin intolerance. Therefore, a pragmatic approach is needed.

Evidence-based statin intolerance may be defined pragmatically as “the inability to achieve evidence-based doses of statin therapy.”

Reporting will be important to document that the patient is not on the evidence-based dose because the patient exhibits pragmatic statin intolerance.

The clinical definition needs to be contrasted with the FDA definition. Because there is movement toward a more clinical and pragmatic approach to statin intolerance from other organizations, such as the NLA, the definition must be expanded.

It is because of the ACC/AHA Guidelines that we are now likely to be faced with even more intolerance, as more patients are unable to tolerate those higher recommended doses of statins.

Clinical judgment is a critical component, as more patients are unable to achieve the evidence-based dose of a statin, or a reasonable, evidence-guided reduction in LDL-C.

Q: How stringent does the definition of statin intolerance need to be?

The meaning of statin intolerance is elusive and highly variable, and in the emerging era of patient-centered medicine, statin intolerance should be redefined in that context, consistent with what is seen in the clinic.

It is also equally important to define what statin intolerance is not, because there are patients not receiving statins who might benefit from such therapy, but they have been branded as intolerant.

Q: Is statin intolerance absolute or does it exist on a spectrum?

Dr. Kopecky: There are 3 broad groups of statin-intolerant patients:

- The first group includes those who take a statin and experience symptoms; the symptoms go away when the drug is discontinued, but return when they restart another drug. This is the statin-intolerant patient.
- The second group of patients has every ache and pain in the world, regardless of the drug they are prescribed.
- The third group includes the patient who will not even begin the statin because they do not want to be statin intolerant. This is the largest group of patients that needs to be addressed—those who refuse the statin outright. These patients are already well informed about possible side effects, so what must be taught are the benefits a statin might provide.

Q: Do you have a treatment algorithm in place?

The panel was in agreement that the Figure 1, as recently published in the *Journal of Clinical Lipidology*,⁴ is representative of an appropriate algorithmic approach.

In addition to this, every algorithm should have a question relating to statin response in family members, as there could be genetic determinants with a familial component, both in terms of response to statins and the potential for adverse events. Although there is not a specific test that can be ordered, heritability is an additional factor to consider.

Q: What are patients willing to tolerate with respect to muscle pain?

Stiffness in a pattern similar to that seen with arthritis does occur with statins, in opposition to a broad general opinion that it does not occur.

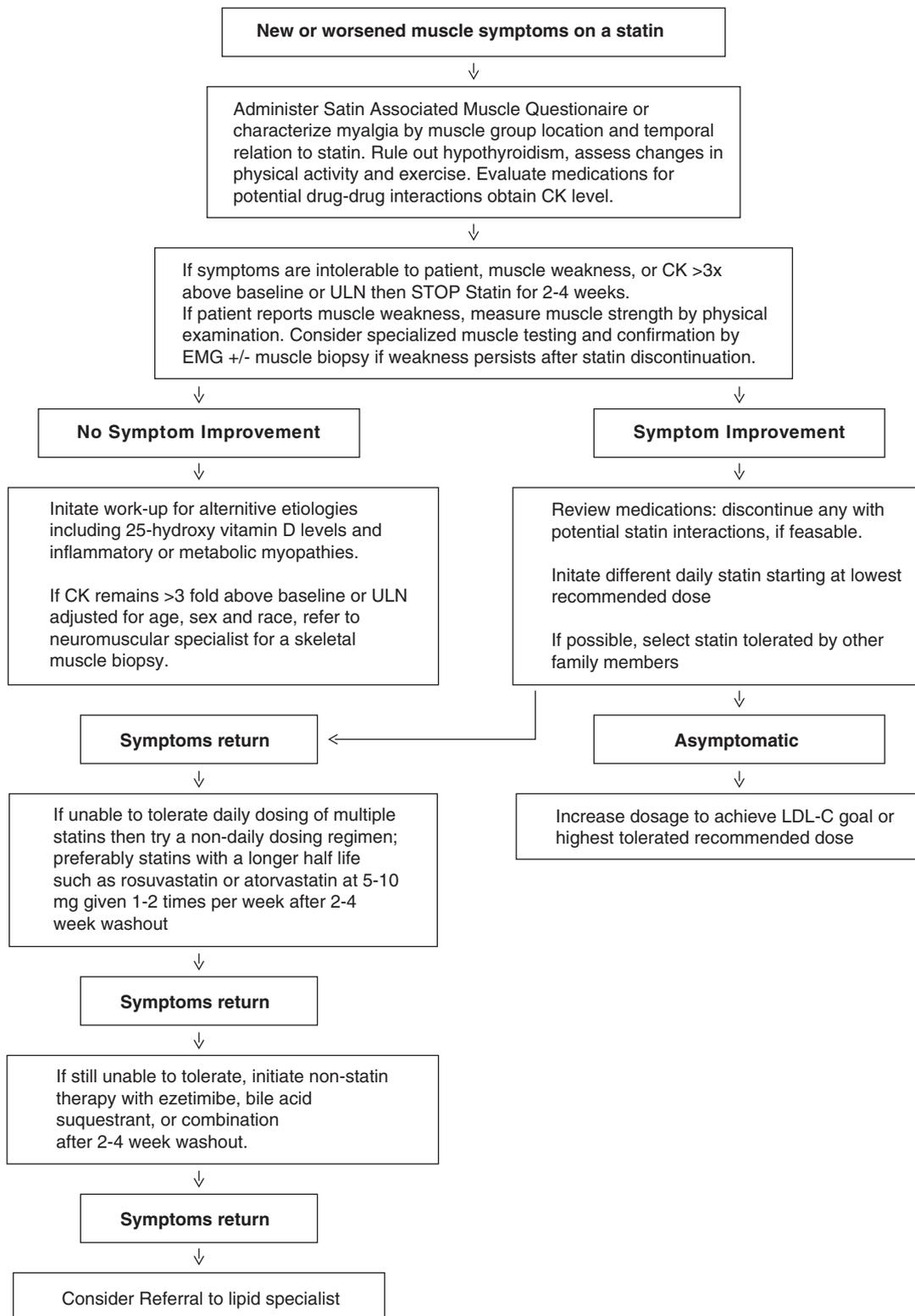


Figure 1. Algorithm for the evaluation of statin-associated muscle injury, as described by Rosenson et al.⁴ Abbreviations: CK, creatine kinase; EMG, electromyography; LDL-C, low-density lipoprotein cholesterol; ULN, upper limit of normal.

It may be detrimental to describe myalgia for patients with brochures and pamphlets, as it then becomes a self-fulfilling prophecy.

There are reporting biases that emerge; when asked if they are experiencing aches and pains, most patients will respond in the affirmative.

Q: Should patients accept muscle pain from statin use?

Dr. Wong: Consider niacin, for example; if a patient experiences flushing on niacin, that means the drug is working. The question then becomes: At what level should muscle pains be considered intolerable if the patient is expecting them to occur?

It is important to differentiate between myalgia, myositis, and rhabdomyolysis; even if a patient has myalgia in the absence of CK elevations, if they simply cannot tolerate the statin, that is statin intolerance.

Q: If a patient is intolerant of one statin, is it appropriate to try another?

Often, many different statins must be tried before success is achieved, in opposition to the opinion that 2 to 3 is the maximum that should be tried.

The specific definition is the inability to tolerate ≥ 2 statins, 1 at the highest prescribed daily dose, and the second at any daily dose. That is the current regulatory and clinical-trial definition. It is a problematic definition, because 2 iterations may not be enough, given the heterogeneity of response among individual patients.

The definition should require more than one re-challenge and more than 1 product, barring extraordinary circumstances.

Most patients are able to tolerate some statin at some given dose.

Q: Are patients willing to try another statin after experiencing intolerance with the first?

Patients must be better educated, particularly as to the benefits of statin therapy in high-risk patients in relationship to the risks of therapy.

Both patients and clinicians should be aware that intolerance to a single statin is not a reason to abandon this strategy. It is important to be patient and persistent, and in most instances, a reasonable approach to care will emerge, even if it departs from the ACC/AHA Guidelines recommendations or conventional approaches. It is important to emphasize that the patient is not immediately deemed intolerant; there is a next step.

Many patients are willing to try another statin after failing the first. To get them to do so, the doctor and patient must engage in a considered and careful discussion regarding both interstatin variability as well as the benefits of statin therapy.

Q: What do you tell a patient about a second statin?

There are variations in response to statins. It must be emphasized to patients that just because they have taken one statin and were intolerant does not mean they will be

intolerant to another statin. The patient should talk to his or her health care provider for additional options.

Dr. Koren: Physicians must be proactive in asking about symptoms, and the use of open-ended questions can be a valuable tool for this, either at the beginning of the session or at the conclusion of the session.

An important question apart from “How are you doing?” is “What are you doing?” This type of question helps tease out information about exercise regimens and activity levels.

Additional questions include “Are there any medicines that you skip?” and “What do you do if you miss one?” These types of questions can open up a dialogue about adherence that might not arise otherwise.

It is important to let the patient know that adherence issues are quite common and that they should feel comfortable discussing these types of issues without any fear of judgment. Let them know what to do if they skip a dose, as many will double up, and that is not appropriate.

Q: If you do not choose to prescribe another statin in these patients, what therapies do you typically prescribe?

The ACC/AHA Guidelines state that if a patient is intolerant to statin therapy, proceed to another evidence-based approach for treatment that is independent of statins. For all patients, the clinical approach will depend upon their specific risk for atherosclerotic cardiovascular disease.

Q: Are patients with statin intolerance still able to achieve the treatment goals that have been set for them?

In regard to the concept of LDL-C targets in relation to statin intolerance, a physician may be faced with the conflict of achieving their desired goals in the face of intolerance. Unique challenges will arise frequently in this population, and the ACC/AHA Guidelines are recommendations; they are not mandates and are not intended to replace clinical judgment.

There are alternative drugs that can be prescribed to lower LDL-C, in particular niacin, bile acid sequestrants, and cholesterol absorption inhibitors (eg, ezetimibe). The latter has been shown to provide added efficacy in terms of cardiovascular disease event reduction over simvastatin in acute coronary syndrome patients in the recent Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) clinical trial (presented at AHA in November 2014).

Q: What diagnostic code do you use for statin intolerance?

Statin intolerance is a very broad clinical issue, but there is nothing in the electronic records to document this, so outcomes research is difficult to quantify.

The enormity of the problem is probably under-recognized, as there is no way to capture this either in the coding or in the billing.

Electronic health records may have it in the problem list, but it is not captured with a specific code. It is not an allergy, and it is oftentimes misclassified as an allergy.

It would be beneficial to have a diagnostic way to place these patients into a specific category. The key is that it be billable, to cover time and effort.

There should also be a recommendation for reporting. The prevalence of statin intolerance is one of the key questions drug manufacturers have, but it is very difficult to actually find the supporting data.

Dr. Koren: It is largely unknown how many patients are not appropriately re-challenged, or are placed onto a lower, nontraditional dose, as it is very difficult to even order a nonstandard dose. In this way, current electronic medical systems may even be considered as somewhat detrimental to the patient.

Q: Is it safe to continue statins in the presence of any degree of intolerance?

There are multiple levels here. There are patients whom we can get onto a statin at a reasonable dose, but it is just not enough to get them where we want them to be with respect to their LDL-C level. These patients are not taking the evidence-based recommendation.

There is actually a fairly small population that cannot tolerate a statin of any kind at any dose. Conversely, there is a very large population of patients that cannot tolerate a high-intensity statin regimen across the board.

Some patients think they will get diabetes out of the blue, and patients are having their statins stopped when they develop diabetes. This actually seems like more of a reason to keep the patient on the statin, and there is almost never a situation where a physician would stop a statin because a patient has crossed a threshold into diabetes; they should intensify their efforts at treating the diabetes. Many of these patients are prediabetic and would have developed diabetes even if not on a statin. The issue here is net clinical benefit associated with preventing cardiovascular events.

Close examination of the data seems to reveal that it is not so much the dose as it is the blood level that corresponds to side effects, and women are typically smaller; an 80-mg dose to a man is fundamentally different from an 80-mg dose to a woman.

Given the lower body size in most women, there may be a greater likelihood that they will not tolerate the recommended doses of statins from the current ACC/AHA Guidelines.

Referral to a lipid specialist should be considered following a determination of statin intolerance.

Q: What are your thoughts on inclusion criteria for clinical trials for statin intolerance?

There are many gaps in our knowledge because of the way clinical trials have been designed in the past.

The first study with atorvastatin (Lipitor) in patients with hypercholesterolemia was a bold, dose-ranging study, and in those days there was some concern with an 80-mg dose; but the study proved to be very successful, with efficacy across the board.

In regard to past clinical trials, the terms “myopathy” and “myalgia” were commonly used, and part of the problem was the lack of a clear definition for these.

Because the constructs of the ACC/AHA Guidelines were so evidence-based, very few statin-intolerant patients were ever included in clinical trials, so there is very little evidence for this group.

Clearly the trials do not include enough women, constituting an important gap in our knowledge base.

The excluded group still needs to be cared for, but this is also a group for which there are very few answers backed by solid data. Aggressive, moderate- to high-intensity treatments that achieve the best responses are important to these patients, and this will require more focus in terms of research efforts and novel therapies and approaches.

In the Literature

Q: How will the new ACC/AHA Guidelines impact statin intolerance treatment?

Dr. McKenney: It is important to recognize that these are really the first American guidelines to discuss statin intolerance in a fully recognized form, with documentation.

The new ACC/AHA Guidelines highlight a meaningful discussion about both the benefits and the potential risks of therapy, and patients should be educated in both aspects of therapy.

Statin use remains a decision that is made between the doctor and the patient, and only after a “risk discussion” about the pros and cons of starting statin therapy and a discussion of nonpharmacologic means to lower LDL-C and other cardiovascular risks.

Q: How do the new ACC/AHA Guidelines impact the perception of statin intolerance as a diagnosis?

Dr. Koren: In general, statin intolerance may be more common than is traditionally appreciated, particularly in view of the new ACC/AHA Guidelines. As the new ACC/AHA Guidelines are better understood and begin to be adopted, the concept of statin intolerance becomes more important to recognize and to figure out strategies for patients at risk.

Dr. Baum: The ACC/AHA Guidelines will likely increase the incidence of statin intolerance, and some physicians may respond by starting with lower doses as opposed to losing that patient at the outset. This strategy is consistent with the ACC/AHA Guidelines, however, and with a patient-centered approach.

The ACC/AHA Guidelines advise, in individuals intolerant of the recommended intensity of statin therapy, to use the maximally tolerated intensity of statin.

Q: What are your thoughts on the findings of the NLA Task Force on Statin Intolerance?

The NLA Statin Intolerance Task Force has similarly presented a pragmatic definition of statin intolerance: “Adverse symptoms, signs and/or laboratory abnormalities attributed by the patient and/or provider to a statin, and perceived by the patient to interfere with daily life activities.” These include predominantly muscle-related symptoms, with muscle aches being the most common, but also may include other symptoms, liver-enzyme increases, and isolated muscle-enzyme increases.

Importantly, the NLA has included the phrase “real or perceived” in further describing these symptoms.

The NLA provides practical, patient-centered recommendations that serve as an important augmentation to the ACC/AHA Guidelines.

The NLA Task Force concluded that statin intolerance requires a patient-centered approach in practice; reducing the dose of statin, switching to a different statin, and alternate regimens, such as every-other-day dosing, are recommended for patients with statin intolerance. For patients who cannot tolerate a statin using the above strategies, alternate agents alone or in combination may be considered; innovative approaches to research on statin intolerance are needed.

Conclusion

There are many who do not recognize the importance of statin intolerance, or even that it requires a well-designed, patient-centered approach. Statin intolerance is common, complicated, and requires a pragmatic approach. It requires persistence, it represents a pool of patients at enhanced risk that have been under-represented in clinical trials, and it represents an opportunity for further evaluation of nonstatin therapeutics. Given the new ACC/AHA Guidelines, statin intolerance may become even more prevalent because of more proactive recommendations to use moderate or intensive statin therapy and the greater number of primary-prevention patients that now qualify for, and may be considered for, statin therapy.

The ACC/AHA Guidelines for treatment of blood cholesterol provide an important foundation for understanding

who might benefit from statin therapy and should form the basis of our treatment approach. It is also important to understand, however, that the ACC/AHA Guidelines afford a clinician the freedom to make decisions in collaboration with their patients and to use clinical judgment based upon the available evidence. The aspects of clinician judgment, interaction with the patient, shared decision-making, and patient-centered care must all be emphasized within this context.

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