The official journal of the Japan Atherosclerosis Society and
the Asian Pacific Society of Atherosclerosis and Vascular Diseases

Editorial

J Atheroscler Thromb, 2019; 26: 403-405. http://doi.org/10.5551/jat.ED106

Statin Intolerance and Suboptimal Statin Therapy

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See article vol. 26: 408-431

Statin Intolerance

In any preventive guidelines on atherosclerotic cardiovascular diseases (ASCVD), statins are recommended as the first-choice medication to reduce the low-density lipoprotein (LDL) cholesterol levels, based on numerous randomized controlled trials. However, there is a certain number of individuals who exhibit "statin intolerance." Although no diagnostic criteria exist at this point, statin intolerance is a well-recognized term, used to describe the situation where a patient needs to discontinue an effective dosage of statin, usually due to muscle symptoms. The first case of statin intolerance was described soon after the discovery of statin by Dr. Akira Endo. An extremely high dose of mevastatin was administered to a 17-year-old girl with homozygous familial hypercholesterolemia, and side effects, including muscular weakness at the proximal parts of the extremities with an elevated level of serum creatine phosphokinase, and glutamate-pyruvate transaminase and glutamate-oxaloacetate transaminase activities were documented[1]. It is of vital importance to understand the prevalence of patients with such statin intolerance. In their article, Kajinami et al. used electrical medical records trying to estimate the frequency of statin intolerance as well as the attainment rate of guidelines among the patients with ASCVD using three different definitions[2]. Despite the study limitations, patients covered by Definition 1 could be considered as having "highly likely statin intolerance," patients covered by Definition 2 as having "potential statin intolerance," and patients covered by Definition 3 as having "probable statin intolerance." The authors found that the attainment rates of target LDL cholesterol/non high-density lipoprotein (HDL) cholesterol levels were significantly lower in patients suspected as having statin intolerance, regardless of definitions. It has also been shown that the attainment rate of the LDL cholesterol target level was lower in the higher risk group[3]. This situation could be at least partially explained by the presence of statin intolerance, hence other emerging options, including cholesterol absorption inhibitors, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, and a new fibrate could be considered.

Known Risk Factors of Statin Intolerance

Based on clinical trials and observational studies, several risk factors for statin intolerance have been detected[4]: age, female sex, small body frame and frailty, multisystem disease, chronic kidney disease, hypothyroidism, alcoholism, grapefruit juice consumption, major surgery or perioperative period, excessive physical activity, history of myopathy while receiving another lipid-lowering therapy, history of creatine kinase elevation, unexplained cramps, family history of myopathy, family history of statin-induced myopathy, and antidepressant use. In addition to those clinical factors, a small study illustrated that a single nucleotide polymorphism encoding the organic anion-transporting polypeptide 1B1, which has been shown to regulate the hepatic uptake of statins was strongly associated with an increased risk of statin-induced myopathy[5]. Some scoring systems using those factors may eventually be useful for risk prediction of statin intolerance.

Nocebo Effect of Statin Intolerance

In 2017, an interesting paper was published illus-

Key words: **Statin, Dyslipidemia, Statin intolerance, Optimal medical therapy**

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Received: October 22, 2018 Accepted for publication: October 22, 2018

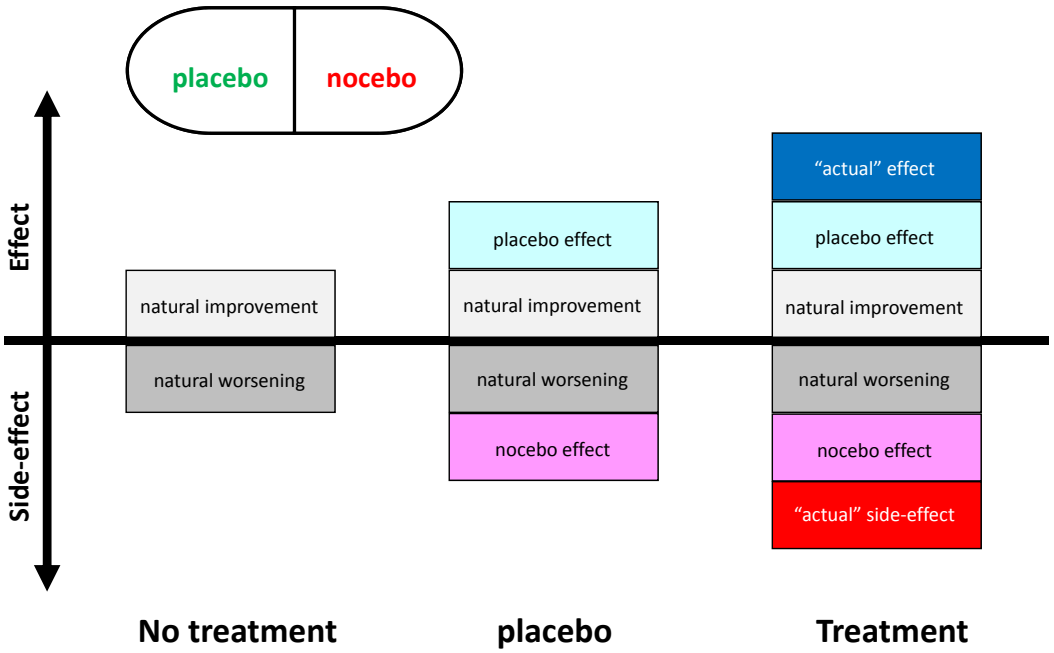

Fig. 1. Scheme of placebo and nocebo effects in medical treatment

Upper side represents effects by natural improvement, placebo effect, or actual effect.
Lower side represents side-effects by natural worsening, nocebo effect, or actual side-effect.

trating the so-called nocebo effect, with an excess rate of muscle-related adverse events only when patients and their doctors were aware that the statin therapy was being used and not when its use was blinded (**Fig. 1**)[6]. These results will help assure both physicians and patients that most adverse events associated with statins are not causally related to use of the drug and should help counter the adverse effects of exaggerated claims about statin-related side-effects on public health. We need to keep in mind this important as well as frequent situation, leading to suboptimal medical therapies.

Conclusion

Regardless of its definition, statin intolerance is an important phenomenon, leading to a poorer control of the LDL cholesterol levels among high-risk Japanese patients. We need to understand the risk factors, as well as the potential nocebo effect, so that we can accurately discriminate the *pseudo statin intolerance* from *true statin intolerance* and reduce their LDL cholesterol more effectively using the golden standard drug. Alternatively, we could consider using other LDL-lowering therapies, such as ezetimibe, PCSK9 inhibitors and fibrates, or some agents that have been shown as add-on/alternative therapies to statins, such as certain nutraceuticals, or coenzyme Q10[7-9].

Acknowledgments

None.

Conflict of Interest

Hayato Tada received a research grant from Sanofi. K.K. Masa-aki Kawashiri received lecture fee from Amgen Astellas Biopharma K.K. and Astellas Pharma Inc, and received a research grant from Bayer Yakuhin Limited and Daiichi-Sankyo Company.

Sources of Funding

None.

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