Statins, Immunomodulation, and Infections: A Complex and Unresolved Relationship

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(See the major article by Antoniou et al on pages 350–6.)

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Statins are now among the most widely used drugs in the world. They have proven efficacy in treating hyperlipidemia and in the prevention of vascular disease, with randomized data showing that they confer benefits in terms of clinical outcomes, including mortality. However, no drugs are without their adverse effects. The most well-known adverse effect of statins is probably muscle toxicity, which led to the worldwide withdrawal of cerivastatin. More recently, the use of statins has been linked to the occurrence of type 2 diabetes [1].

In this issue of Clinical Infectious Diseases, in a population-based cohort study of individuals aged ≥65 years, Antoniou et al [2] show that the use of statins was associated with a higher risk (hazard ratio, 1.13 [95% confidence interval, 1.10–1.17]) of reactivation of latent varicella-zoster virus (VZV) infection. Although the absolute risk was low, the attributable fraction was high, with the authors estimating that 20 000 cases of herpes zoster per year in the United States could be attributable to the use of statins. However, before one accepts the findings and recommendations, it is important to evaluate strengths and limitations of the study, as well as the underlying biological rationale.

The strengths of the study include the use of a well-characterized database that has been widely employed for pharmacoepidemiology studies; the careful design with adequate numbers of subjects who were exposed to statins and subsequent events; and the use of propensity analysis, a balancing score to ensure that the cases and controls are well matched at baseline [3], to reduce the risk of confounding. However, in any observational study, there is a residual risk of unforeseen confounding, particularly when the risk is as low as 13% above baseline. Some limitations of the study include the inability to define a dose-response relationship as most patients did not have a change in dose, and the use of statins as a class, as the individual compounds vary widely in their physical properties and pharmacokinetics and thus may have differential effects.

What about the underlying biological plausibility? Statins are known to have multiple modes of action [7]. Furthermore, they are likely to vary between individuals because of differences in underlying
comorbidities, concomitant drug therapy, and individual factors including age. It is known that cell-mediated immunity, which protects against VZV reactivation, tends to wane with age [8]. Statins have immunosuppressive properties, and thus much like steroids and anti–tumor necrosis factor (TNF) agents [9], could predispose to reactivation of VZV. However, the immunosuppression caused by statins is clearly not as pronounced as that seen with steroids and anti-TNF agents [9], but whether this varies in different individuals is unclear. Given the pleiotropic effects of statins, it is thus theoretically possible that they could cause reactivation of VZV in predisposed individuals.

The final issue to consider is the role of cholesterol itself. A study of 12 patients after heart transplant showed that patients who developed herpes zoster had higher cholesterol levels within 1 month of the episode compared to controls [10]. There are no studies examining the relationship between serum cholesterol levels and VZV, and unfortunately, the study by Antoniou et al [2] did not have data on serum cholesterol prior to the development of herpes zoster.

In summary, Antoniou et al [2], in a well-conducted study, have shown that statins may have the potential to cause VZV reactivation, but because of the issue of confounding and the lack of a definitive mechanism, there is a need for replication of the study findings in a different pharmacoepidemiologic database. The authors [2] also suggest the use of herpes zoster vaccine in patients requiring statin therapy. Indeed, this is already recommended in elderly patients irrespective of statin use. For instance, the US Centers for Disease Control and Prevention currently recommends that the vaccine should be used in all patients aged >60 years, and the UK Department of Health has recently recommended the use of the vaccine in patients aged >70 years. The take-home message is that statins are still a highly beneficial group of drugs in patients with atherosclerotic arterial disease, and their use in any patient group should be based on a careful evaluation of the individual benefits and risks.

Note

Potential conflicts of interest. Author certifies no potential conflicts of interest.

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References