Shingles and Statin Treatment: Confounding by Cholesterol or APOE4 Status?

To the Editor—In a large cohort, Antoniou et al report a 13% increased risk of herpes zoster among statin users compared with nontreated individuals [1]. The relationship between herpes zoster and statin treatment is probably complex [2], and we would like to offer a further view to this conundrum.

Identifying possible new adverse effects is important, but on the other hand, great care must be used when drawing conclusions from observational studies. The large numbers of statin users worldwide also make possible spurious associations without the existence of cause and effect. This seems to be the case in the recent association between statins and cataracts in a population cohort [3], where confounding by indication—longer cholesterol burden among statin users—may explain the epidemiological association, not confirmed in clinical trials [4].

Despite the careful propensity score matching and comparison with knee arthroplasty in the study by Antoniou et al, we believe there still is a possibility for confounding by indication or through the carrierness of the apolipoprotein E epsilon 4 allele (APOE4). There was no matching for cholesterol levels nor APOE4 in the study by Antoniou et al.

According to our counter-hypothesis, herpes zoster risk is increased among statin users because these individuals have higher than average serum cholesterol levels and higher than average frequency of APOE4. High serum cholesterol levels have been associated with herpes zoster in one study [5], and there are several reports on the connection of APOE4 with immunity against Herpesviridae [6, 7].

Intestinal cholesterol absorption is known to be increased in individuals with APOE4, reflected in their higher serum cholesterol levels [8], but the connection between APOE4 and Herpesviridae is less well known. Sufferers of cold sores, skin presentations of herpes simplex 1 activation (herpes simplex labialis), are more often APOE4 carriers than non-carriers [6]. There are scarce and conflicting data from small studies about a connection between APOE4 carrier status and herpes zoster [9, 10], but a similar mechanism between cold sores and shingles (activation through peripheral nerves) makes the connection plausible. Higher cholesterol levels observed in patients with herpes zoster in one study support the link between APOE4 and herpes zoster [5]. Conversely, because there hardly is any association between serum cholesterol or APOE4 with probability of knee arthroplasty, it is no wonder that there was no association with statin treatment.

Of the variables in Table 1 by Antoniou et al, overall cardiovascular disease burden seems to be higher among statin users; for example, myocardial infarction and angina were more common in statin users than controls (5.8% vs 4.5%, and 7.7% vs 6.3%, respectively) Although the absolute differences are small, the data indicate that the risk factors for vascular events are not equally distributed in the 2 groups (29% more myocardial infarctions and 22% more angina in the statin group).

Thus, is there a causal link between statins and herpes zoster? Do the authors have any data on cholesterol levels or APOE4 in their cohort to confirm or refute our hypothesis?

Note

Potential conflicts of interest. T. E. S. has had educational, consultative, and research roles with various companies marketing statins (now generic in Finland), and a small amount of stock of a listed company, Orion Pharma, which also markets generic statins. P. T. reports no conflicts of interest.

Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.
Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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References