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LETTER TO THE EDITOR

Statin therapy and herpes virus reactivation—response to Zuin et al. paper

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Dear Dr. Van Belkum,

We read with interest the article by Zuin et al., "Herpes zoster infection and statins: which implications in clinical practice?" [1]. It is an interesting and well-researched paper. There are only a small number of papers however, which address the potential association of statins with herpes reactivation, mostly without confirming a dose effect, and conclusions must be tempered with these particular limitations.

If we apply the mathematics of a meta-analysis to these studies, the combined effect size (CES) of the case control studies infers no association between statin use and risk of herpes infections [2–5]. Heterogeneity is very high > 98% (I^2) meaning prediction intervals are difficult to interpret however. Kim et al. [4] (whose rigorous study discusses the limitations including sampling bias) take their cases and controls from different populations. Despite propensity score matching for conditions including cardiovascular disease, there is no statin use in the control group, which must infer that the control population is an undertreated group with vascular disease, diabetes, and hypertension who are not being prescribed statins [4].

Meta-analysis of the cohort studies (Fig. 1) again shows no effect of statin use and herpes infection with a CES odds ratio of 1.15 (0.80–1.47) [6, 7]. Heterogeneity in the cohort studies was lower than the case controls at 34%. However, the funnel plot shows deviation around the average (Fig. 2) and this level of heterogeneity is still too high to be able to interpret the CES with any confidence. The prediction interval is 0.82–1.61, but again there is likely to be sampling bias here accounting for the heterogeneity.

The meta-analysis failed to show a strong association between statin use and herpes infections with odds ratio confidence intervals crossing 1.0 and high heterogeneity rendering firm conclusions difficult. The heterogeneity may arise due to the variation in country of origin of the patient and the small number of studies and so the meta-analysis is a force-fit model and further biases the outcome. There are significant differences between the prevalence of cardiovascular disease, lifestyle, and access to healthcare between these populations [8, 9]. We have also not accounted for publication bias. Furthermore, each study is limited by lack of a robust diagnostic method, relying on clinical diagnosis alone. All studies treated statins as a class rather than individual drugs and there was a paucity of data in regard to the following:

- Dosages of statins,
- Whether a patient was on the statin at the time of reactivation,
- Duration of treatment,
- Confirmation of concordance with therapy,
- Cholesterol levels,
- Confounding factors such as sunlight exposure [10].

However, the limitations are balanced by the large number of patients included in some well-designed studies but none checked concordance. Interestingly, Kim et al. [4] did show a duration- and dose-based increase, which would support the hypothesis that statins might increase the risk of herpes reactivation, but this was not shown by others.

One must consider the risk of cardiovascular events when discussing the adverse outcomes of statins. Choosing your patient group is important, as we will demonstrate in the rest of this paragraph. In familial hypercholesterolaemia, for example, the absolute risk of first onset coronary heart disease was 119 per 1000 person years in untreated patients, which drops to 11 per 1000 person years in the statin-treated group

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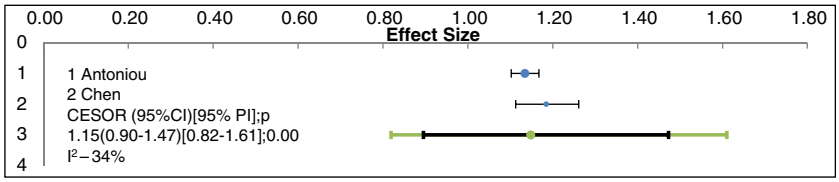

Fig. 1 Meta-analysis of the cohort studies assessing statin use and herpes infection risk. The meta-analysis shows no effect of statin use and herpes infection with an odds ratio of 1.15 (CI 0.80–1.47). Heterogeneity (I^2) in the cohort studies was less than 34%

[11]. If we do not prescribe statins to these groups of patients, or prevent compliance by warning them of potential herpes reactivation, we would get 108 myocardial infarctions per 1000 years (which excludes stroke and peripheral vascular disease) compared to, for example, Kim et al. demonstrating 1.4 episodes of herpes reactivation per 1000 person years with statin use [4]. Another set of calculations for the same group of patients with familial hypercholesterolaemia suggests that if we compare optimal dose of statins versus no treatment over a lifetime (30–85 years of age) we would be able to prevent, per 1000 treated patients, 141 myocardial infarctions, 262 strokes, 142 heart failures, and 101 cardiovascular deaths [12]. If we were to look at a different group of patients, e.g., diabetics and primary prevention, the incidence of major coronary events was 16.7 per 1000 patient years in the no statin group and this drops to 11.0 per 1000 person years if they are given simvastatin [13], a less striking drop compared to those with familial hypercholesterolaemia but still serious as the major coronary events included death.

Forbes et al. looked at the effect of certain comorbidities on the risk of herpes zoster in a case control study with 144,959 cases and 549,336 controls in the UK [14]. Although statin use was not included specifically, diabetes was included in the study. Statins are a cornerstone of diabetes management and reassuringly diabetes had the lowest increase in risk of herpes of any of the other included comorbidities with an odds ratio of 1.02 in a fully adjusted model (95% CI 0.99–1.05). This may suggest that statins do not increase risk more than conditions associated with inflammation or immunosuppression; however, the rates of statin use in any group were not recorded.

In conclusion, meta-analysis of the data currently available does not support a link between herpes infections and statins. Though adverse drug reports for herpes in statin use exist, they are infrequent and do not prove causation. As VZV vaccination schedules in the UK depend on age rather than a statin drug history, we cannot recommend that vaccination use is promoted based on the data presented here. Nor can we recommend that concerns about herpes should affect statin prescription decisions, particularly in high-risk group patients where the sequelae of untreated hypercholesterolaemia include death.

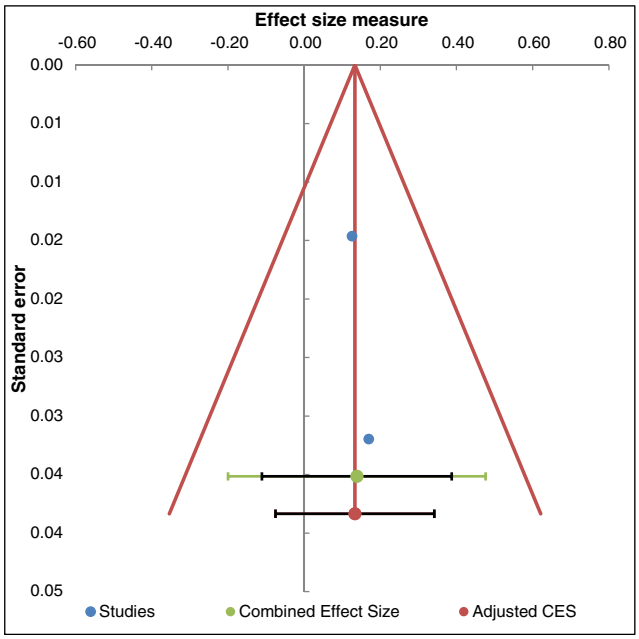

Fig. 2 Funnel plot of the cohort studies assessing stating use and the risk of herpes infection. The funnel plot shows deviation around the average

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