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Title: Association Between Early Severe Cardiovascular Events and Ustekinumab Treatment?—Reply

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We thank Gelfand *et al.*¹ for their interest in our study.² Their main criticism relates to the appropriateness of the case-crossover design, while our study used a case-time-control design. The case-crossover design is however an adequate theoretical framework to discuss their objections to our study. Gelfand *et al.* refer to two concepts related to time that merit clear distinction.

The first concept is the “transience of effect”. We are concerned about a misunderstanding on the very question addressed in our study: we addressed the hypothesis of severe cardiovascular events being associated with ustekinumab *initiation*. If there is an initiation-related effect, it is, by definition, transient: after some time has passed, the effect possibly related to initiation fades, and a cumulative effect takes over. Distinguishing these two types of effect (transient and cumulative) “can be of great importance, especially in the rare situation that the transient and cumulative effects are in opposite directions”, as pointed out by Maclure *et al.*³

The second concept is the “induction time”, *i.e.* the time necessary for the effect to develop, and this translates into the choice of an exposure window. The time window is derived from the time frame necessary for the exposure-related effect to trigger the outcome. Time windows in case-crossover studies can extend as far as “1 year before the outcome event”.⁴ Given the hypothesized immunological mechanism (immuno-mediated atherosclerotic plaque destabilization), a “just before” time window (if this means “measured in hours or days”) would have been inappropriate. Our 6-month risk period was justified by a hypothesized underlying biological mechanism, and pre-specified in the protocol.

Beyond these considerations on the case-crossover design, we acknowledge that the observed events are rare and the confidence intervals for the odds-ratios are consequently large. Only large databases can evidence such differences for rare events, and we see this as a strength of our study. The unavailability of clinical and biological (“conventional”) cardiovascular risk factors is a limitation of our study. However, the issue was to distinguish high- and lower-risk populations, based on a pre-specified hypothesis of an association between severe cardiovascular events and ustekinumab initiation, anticipated to occur exclusively among patients with high baseline cardiovascular risk.

We would like to stress that our study addresses the general question of “why now”, and not “why me”,⁵ for severe cardiovascular events among patients with high baseline cardiovascular risk at the time of ustekinumab initiation.

Overall, our findings point to the need for clinicians to be aware of the risk of severe cardiovascular events within 6 months after ustekinumab initiation among patients with high baseline cardiovascular risk (while this does not preclude any type of long-term cardiovascular effect). They also point to the need for epidemiologists and immunologists to study similar risks with other biologics targeting the Th17 pathway.

Conflict of Interest Disclosures: None

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