

Association of ustekinumab and briakinumab with major adverse cardiovascular events

An appraisal of meta-analyses and industry sponsored pooled analyses to date

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Safety concerns have been raised regarding possible association of major adverse cardiovascular events (MACEs) with use of anti-IL-12/23 biologic agents for the treatment of chronic plaque psoriasis (CPP). Ten MACEs have been recorded in actively-treated patients during the placebo-controlled phase of phase II and III studies compared with zero events in placebo-treated patients, along with a total of 53 MACEs (26 ustekinumab, 27 briakinumab) and five cardiovascular deaths (1 ustekinumab, 4 briakinumab) across all phases of these studies. Two industry-independent meta-analyses of randomized, double-blind, placebo-controlled, monotherapy trials calculated risk for MACEs. One detected statistically significant increase in cardiovascular risk using Peto method ($p = 0.04$), while the other utilized Mantel-Haenszel fixed-effects model with absolute risk differences as effect measure, but did not achieve significance ($p = 0.11$). Statistical theory reports that Peto method is more suitable for meta-analyses of studies with baseline event rates of 1% or less and randomization ratios ranging from 1:5 to 1:1 as is the case in these meta-analyses. Potential of anti-IL-12/23 biologic agents to further increase cardiovascular morbidity cannot be excluded and a class effect cannot be denied. Clinicians should screen CPP patients for manageable cardiovascular risk factors before initiating anti-IL-12/23 agents along with intensive monitoring of these patients.

Safety concerns have been raised regarding the possible association of major adverse cardiovascular events (MACEs) with the use of anti-IL-12/23 biologic agents (ustekinumab, briakinumab) for the treatment of chronic plaque psoriasis (CPP). Ten MACEs (5 ustekinumab, 5 briakinumab) have been recorded in actively-treated patients during the placebo-controlled phase of phase II and III studies compared with zero events in placebo-treated patients, along with a total of 53 MACEs (26 ustekinumab, 27

briakinumab) and five cardiovascular deaths (1 ustekinumab, 4 briakinumab) across all phases of these studies.^{1,2}

Two industry-independent meta-analyses of these 9 randomized, double-blind, placebo-controlled, monotherapy trials^{3–11} have been recently conducted to examine the possible association of MACEs with anti-IL-12/23 agents.^{1,2} Ryan et al. did not detect a statistical significant increase using the Mantel-Haenszel fixed-effects model with absolute risk differences as an effect measure, although their findings approached significance ($p = 0.11$).¹ In contrast, Tzellos et al. detected a statistically significant increase in cardiovascular risk using the Peto method ($p = 0.04$), which excluded studies with zero events.² An astute reader may wonder how there could be divergent results between these two meta-analyses which essentially use the same data. The divergence in results between these two meta-analyses may be attributable to the use of the risk difference method in the first study.¹ The risk difference method provides estimates for all studies, including zero event studies, using zero-cell corrections, but yields a very conservative confidence interval coverage when events are rare, potentially resulting in low statistical power. This may make this method less suitable for meta-analysis of rare events.^{12–14} Mantel-Haenszel methods also involve the use of an arbitrary numerical correction to avoid computational errors that occur when attempting to divide by zero. MACEs event rates were 0.28%, 0.35% and 0.31% for ustekinumab, briakinumab and both agents respectively.² It has been demonstrated that at a baseline event rate of 1% or less, Peto method has the best performance among all meta-analytical methods considered; as Peto is a more powerful method it is more suitable to exclude a possible higher risk for MACEs in the treatment arm compared with placebo.¹² Additionally, when events are rare, odds ratios are in fact very close approximations to relative risks. Calculation of the Peto odds ratio did not necessitate the data of 5 out of 9 studies included in the second meta-analysis. One might feel that it is wrong to exclude any studies from a meta-analysis. However, if no events occur at all in a trial, that trial conveys no information about the relative odds or risks of events between the two groups. Since a meta-analysis is practically a weighted average of trial results, with weights reflecting the amount of information

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each study contains about the summary statistic, allocating a trial with no information a zero weight may be appropriate and may not introduce bias. Furthermore, the Peto method aggregates within-trial comparisons across trials while avoiding the need for the arbitrary addition of 0.5 events when no events are observed.

On the other hand, the notion also exists that exclusion of these five trials may be important to recognize as it changes the population under evaluation. Two of the ustekinumab trials that were excluded in the second meta-analysis were conducted in Asian populations,^{5,11} which generally have lower cardiovascular risk, whereas all other studies were conducted in primarily Caucasian populations.^{3,4,6-10} The three ustekinumab trials included in both meta-analysis fail to report a clear method to screen for and capture MACEs. All three briakinumab studies excluded also fail to report a clear method to screen for and capture MACEs. One excluded briakinumab study used the presence of “a poorly controlled medical condition, such as uncontrolled diabetes with documented history of recurrent infections, unstable ischemic heart disease, congestive heart failure, recent cerebrovascular accidents” as exclusion criterion, also leading to possible selection bias and an underestimation of the treatment’s pragmatic effect.⁶ All patients included in the studies had a mean age less than 50 y old. Of note, it has been suggested that the risk for myocardial infarction in psoriasis patients treated with systemic therapies may vary by age with a key time point of 50 y old, separating low from high risk patients.¹⁵ It is also important to note that all individual RCTs included in these meta-analyses were underpowered to detect a statistically significant difference in the rate of MACEs. Although all studies reported that patients were well balanced across treatment groups with respect to demographic characteristics, many of them failed to report baseline cardiovascular risk factors. All studies had a controlled phase up to week 12, except one, with a controlled phase lasting 20 weeks.⁷

There is also a possibility that these methods underestimated the risk. As is the case in most clinical trials, more patients were randomized to the interventional arm than to the placebo arm (aggregate 3179 vs. 1474).¹² Where there is imbalance in treatment arms, application of the Peto method may lead to an underestimation of the event rate in the larger arm (in this case the experimental anti-IL-12/23 treatment arm), whereas biases in estimates of balanced large treatment effects are negligible.¹² Thus, the meta-analysis conducted by Tzellos et al., may have still underestimated the true MACEs rate. While the Peto method has been reported to demonstrate considerable bias when imbalances between patient numbers in the compared arms are 8:1 or higher,¹⁶ all studies of anti-IL-12/23, agents included in the meta-analyses had randomization ratios ranging from 1:5 to 1:1.

In parallel, two industry sponsored pooled analyses^{17,18} have been published, calculating the rate of MACEs in patients treated with ustekinumab in the uncontrolled phases (3 and 4 y of follow-up) of 4 RCTs^{7-9,19} and comparing it with expected rates in the general population using two discrete predictive models. One was developed from the US Framingham Heart Study (FHS) after adjustment for baseline CV risk factors,

including age, gender, hypertension, hyperlipidemia, diabetes mellitus and smoking status. The second predictive model was developed from the UK General Practice Research Database (GRPD). These pooled analyses summarized the rate of MACEs observed for ustekinumab by pooling the safety data across all trials. Comparisons were performed for myocardial infarction and stroke.^{17,18} Both analyses concluded that ustekinumab exhibits neither a detrimental nor a beneficial effect on serious cardiovascular events and that no cumulative toxicity can be detected.^{17,18} All MACEs were retrospectively evaluated by the same committee across both studies. The authors performed simple pooling of the data from all trials as if the data came from a single trial. Simple pooling consists of adding the numbers of events observed in a given treatment group across the trials and dividing the results by the total number of patients included in this group. However, this is problematic as the RCTs included derived from different settings, and although authors report that baseline characteristics were generally comparable across studies, they also report that variability was observed.^{17,18} A stratified analysis may have been less susceptible to potential biases. Furthermore, absence of a control cohort beyond the initial 12–20 week placebo-controlled phase makes comparison difficult. The authors attempted to overcome this issue by comparing incident MACEs rates from relevant but not maternal populations. But it is important to note that the FHS has been documented to overestimate MACEs risk in European Caucasian and Asiatic populations.²⁰⁻²⁸ Therefore, it cannot be concluded that the lower rate of MACEs reported in carefully-selected ustekinumab-treated patients in multinational clinical trials^{17,18} compared with FHS rates translates into a lack of association between ustekinumab and MACEs. Furthermore, although an attempt was made to adjust modeled analyses for possible confounding characteristics or comorbidities when comparing to the FHS, other unrecognized confounding variables and covariates may exist which impact the final results. The GRPD, as a claims database, relies heavily on billing codes, leading to considerable potential for diagnostic misclassification and the possibility of sampling bias. Therefore, as the authors also appropriately acknowledge, caution should be exercised in the interpretation and extrapolation of these results to the psoriasis population in general.

An industry sponsored pooled analysis has been recently published, calculating the rate of MACEs in patients treated with briakinumab in 5 RCTs^{3,4,6,10,29} and an Open Label Extension (OLE) study.³⁰ Two thousand five hundred twenty patients received ≥ 1 dose of briakinumab in a parent study and/or the OLE, contributing 4,704 patient years of follow-up. In this period of time, 27 MACEs (in 26 patients) were recorded. In this pooled analysis population, 36.9% of patients had a CV-related medical history at baseline of their respective parent study while 69.2% of those experiencing MACE had such a history.³⁰ The authors report four cardiovascular factors associated with increased risk for MACE: elevated baseline BP (SBP ≥ 140 or DBP ≥ 90), history of diabetes, history of CVD, and BMI ≥ 30 . Moreover, the authors calculated an eight-fold relative risk for MACEs when at least two of these factors were present. Based on their results, they

conclude that categorizing by ≥ 2 vs. 0 or 1 risk factors results in a medically relevant and meaningful method for possibly distinguishing between briakinumab-treated patients at high and low risk of MACE.³⁰

On review of the current evidence, an increased risk of MACEs with use of ustekinumab and briakinumab cannot be excluded, particularly in the initial treatment-induction phase. In a phase 2 study of ustekinumab, serum levels of the p40 sub-unit of IL-12 were increased paradoxically 13-fold in the first 12 weeks of the treatment with a gradual decrease to above baseline levels at week 32.³¹ This concept suggests the troubling possibility that many anti-cytokine monoclonal antibodies might function as agonists, rather than antagonists, in vivo, at least in the induction phase. Preliminary evidence indicates that IL-12 is proatherogenic. Development of MACEs in the anti-IL-12/23 treated groups could be related to this paradoxical increase leading to instability of atherogenic plaque, especially in patients predisposed to MACEs due to baseline cardiovascular risk factors. All patients with MACEs had at least three baseline cardiovascular risk factors. Although tempting to theorize that these patients would have developed MACEs anyway, caution is warranted due to the fact that the randomized populations in placebo exhibited no MACEs. The hypothesis that treatment with anti-IL-12/23 increases the risk of MACEs, at least in the initial phase, where the probable agonistic effect takes place, especially in CPP patients predisposed to cardiovascular morbidity with baseline pre-existing cardiovascular risk factors is plausible, can be formulated and ought to be tested. In order to test such a hypothesis, adequately powered RCTs with placebo-controlled-phases of sufficient duration and comprehensive baseline cardiovascular risk factor profiling are required, to evaluate the possible effect of ustekinumab and briakinumab on human atherogenic plaque. Recent evidence suggests that inflammatory joint disease may play a role in cardiovascular morbidity in psoriatic arthritis.³² The potential role of psoriatic arthritis in patients with CPP treated with these biological agents in the rate of MACEs remains to be elucidated. However, other known important and independent cardiovascular risk factors like previous smoking status, hypertension, obesity, hyperlipidemia, type 2 diabetes mellitus are available. In order to test the above mentioned hypothesis fully objectively an individual patient data meta-analysis of the RCTs must be conducted, which would ideally use comprehensive patient level data to allow for more statistically robust time-to-event analyses and also identification of possible sub-groups with increased risk of MACEs.³³

Evidence of harm from a clinical intervention is more difficult to establish than evidence of benefit. While the truthful answer

to this question may not be known until we have the results of well designed randomized controlled trials which are adequately powered to detect serious cardiovascular events as primary end points, clinicians must make therapeutic decisions before the results of such trials are readily available. Clinicians must interpret evidence to date in the clinical context that CPP is not a life-threatening disease. If it has a life-threatening component, it is due to the possible increase in cardiovascular morbidity. The potential of anti-IL-12/23 biologic agents to further increase cardiovascular morbidity cannot be excluded and a class effect cannot be denied, until substantial and more conclusive evidence is available. Briakinumab and ustekinumab are both human monoclonal antibodies targeting the same shared sub-unit (p40) of IL-12 and IL-23, belong to the same drug class and in the RCTs included were used for the same indication. They both demonstrate similar pharmacodynamics.

Contemporary evidenced-based medicine demands clinicians use the best available evidence in guiding the care of their patients.³⁴ Notably, evidence is derived from groups, whereas medicine is applied to individuals.³⁵ Inferring individual effects from average group effects can be challenging: a benefit in a summary results of RCTs does not imply that the probability of benefit outweighs the risk of harm for every patient within the trial.³⁵ Ideally, until more definitive data are available, clinicians should screen psoriasis patients for manageable cardiovascular risk factors prior to initiating anti-IL-12/23 agents along with intensive monitoring of these patients. Post-marketing studies and the use of appropriately designed biologic registries are also necessary to monitor the short and long-term cardiovascular safety of anti-IL-12/23 biologic agents and to ensure that safety remains the utmost goal in the systemic and biologic therapy of patients with moderate to severe CPP.

Disclosure of Potential Conflicts of Interest

T.T. has been reimbursed for travel expenses and hotel accommodation to attend Dermatological Congresses by Janssen-Cilag, which produces ustekinumab (Stelara®), by MSD, which produces infliximab (Remicade®) and by Novartis. C.C.Z. has been reimbursed for travel expenses and hotel accommodation and have received a honorary for participating and lecturing at the Advisory Board for hidradenitis suppurativa of Abbott, which produces adalimumab (Humira®). He has also participated and continues to participate at clinical studies on the treatment of hidradenitis suppurativa with adalimumab. A.T. has participated in clinical trials for chronic plaque psoriasis sponsored by Abbott, Janssen-Cilag, Pfizer and MSD. A.K. declares no conflict of interest.

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