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Does biologic treatment of psoriasis lower the risk of cardiovascular events and mortality? A critical question that we are only just beginning to answer

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Previously thought to be just a skin disease, psoriasis, particularly when more severe, is now understood to be associated with an increased risk of cardiovascular (CV) morbidity and mortality. In a prospective, population-based, cohort study of 8760 patients with psoriasis, we found that patients with psoriasis affecting more than 10% of the body surface area had an 80% increased risk of mortality, independent of common risk factors [1]. Furthermore, life expectancy for patients with moderate to severe psoriasis is cut short by 5 years, and CV disease is the most important cause of excess mortality[2].

Given these striking findings, it is critical to determine which treatments, if any, for moderate to severe psoriasis may reduce the risk of major cardiovascular events and mortality. One approach is to conduct observational studies of patients with psoriasis based on data collected in medical records or administrative claims. In this issue of the JAAD, Wu and colleagues from Abbvie (a company that markets the tumor necrosis factor alpha inhibitor (TNFi) adalimumab) leverage the Truven Health Analytics Market Scan Database, a US administrative claims database with information on 25 million employed patients and their dependents from 2000–2014[3]. They explored the hypothesis that TNFi treatment of psoriasis would be associated with a lower risk of major CV events (which they defined as hospitalization for MI, stroke, TIA or unstable angina) compared to phototherapy. They also hypothesized that cumulative exposure to TNFi is associated with a greater reduction in CV events compared to cumulative exposure to phototherapy. They studied 11,410 and 12,433 patients treated with TNFi and phototherapy, respectively; a remarkable example of the power of medical informatics. The TNFi cohort had a lower risk of CV events compared to

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phototherapy (HR 0.77, 95% CI: 0.60–0.99, p=0.046) which became statistically significant as soon as 4 months after treatment initiation. Each six month cumulative exposure was associated with an incremental 11% CV risk reduction in TNFi treated patients compared to phototherapy treated patients (HR 0.89, 95% CI 0.79–0.99, p=0.048). From these data the authors estimate that treating 161 with TNFi instead of phototherapy would be associated with one fewer CV event per year.

As with all studies, there are important limitations to consider. Epidemiological studies are subject to error introduced by the manner in which patients are selected for inclusion in the study (section bias) or monitored for the outcome (information bias)[4]. For example, if patients selecting TNFi were healthier than patients selected for phototherapy then the healthy user effect (a form of selection bias) might explain the protective benefits observed. Such an effect could also explain the apparent incremental benefits with continuous use of TNFi. Patients receiving phototherapy are also likely monitored more closely (as they have more frequent encounters), however, this potential information bias seems unlikely to explain the results given the relatively “hard” nature of the outcomes under study (hospitalization). Confounding, or a mixing of effects by a third variable that is associated with an exposure of interest, and independent of that association, is a risk factor for the outcome being studied, may also result in error in observational studies. For example, if patients receiving phototherapy were more likely to smoke or be obese compared to those receiving TNFi than this imbalance in confounding factors could explain the results. Only about 1% of patients were classified as smokers and 2–3% as obese, which is much lower than expected, demonstrating the limitations of using administrative claims data for epidemiological research. Furthermore, the observation period included the time up to 365 days after treatment discontinuation and thus it is unclear the degree to which risk reduction was attributable to psoriasis treatment. Indeed, the observation period on average was relatively brief (12.6 months for phototherapy and 18 months for TNFi), by CV trial standards, raising questions about the biologic plausibility of the results. Moreover, the magnitude of effects observed was modest, albeit, potentially clinically important, and of borderline statistical significance. Finally, the most clinically significant event, cardiovascular mortality was not evaluated. In isolation, the results of this study might be interpreted as preliminary given the potential for bias, confounding, and statistical error to explain the results. However, the study does add to a growing literature of observational studies in rheumatoid arthritis and psoriasis suggesting that TNFi are associated with a reduction in CV events[5]. In contrast, two recent, well powered RCTs demonstrated no benefit of TNFi on aortic vascular inflammation, however, important inflammatory CV risk biomarkers such as CRP and GlycA were strongly improved providing some experimental evidence of the potential benefit of TNFi on CV events [6, 7]. Critically, a recent randomized placebo controlled trial (CANTOS) of canakinumab, a biologic targeting Il-1 beta, in 10,061 patients with prior MI and elevated CRP demonstrated, for the first time, that immune targeted treatment causes a reduction in major CV events. The overall effect size in CANTOS was comparable to that observed by Wu et al, albeit there was no evidence for benefit as early as after 4 months of treatment, or a cumulative benefit with longer intervals of treatment with canakinumab[8]. Taken together, advances in clinical epidemiology, clinical trials, and translational research provide increasing evidence that immune targeted therapy

may lower the risk of CV disease. Ultimately, randomized controlled trials will be necessary to definitively determine which psoriasis treatments, if any, are most effective at lowering the risk of CV disease and mortality. Despite all of our advances in psoriasis research, we remain at the very beginning of answering this critical question for our patients.

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