

Cardiovascular Comorbidities of Psoriasis and Psoriatic Arthritis: A Report from the GRAPPA 2012 Annual Meeting

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ABSTRACT. At the 2012 annual meeting of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) in Stockholm, Sweden, several GRAPPA members led a panel discussion on cardiovascular (CV) comorbidities of psoriasis and psoriatic arthritis (PsA). The panelists discussed the role of insulin resistance in the pathophysiology of psoriasis, the possible effect of tumor necrosis factor inhibitors on CV comorbidities, and the effect of 12/23 monoclonal antibodies on CV outcomes. The panelists also addressed how lessons from CV comorbidity research could be applied to other areas of comorbidity research in psoriasis and PsA and identified future research directions in this area. (J Rheumatol 2013;40:1434–7; doi:10.3899/jrheum.130457)

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CARDIOVASCULAR COMORBIDITIES PSORIASIS BIOLOGICS PSORIATIC ARTHRITIS
TUMOR NECROSIS FACTOR INHIBITORS COMPARATIVE EFFECTIVENESS

The cardiovascular (CV) comorbidity discussion panel at the 2012 GRAPPA Annual Meeting comprised Drs. Wolf-Henning Boehncke, Joel Gelfand, and Ehrin Armstrong, and was moderated by Dr. April Armstrong. The panel presented recent data regarding CV comorbidities in psoriasis and psoriatic arthritis (PsA), discussed the effects of psoriasis systemic treatment on CV comorbidities, and defined future research directions.

Insulin resistance in psoriasis

Dr. Boehncke discussed the role of insulin resistance in the pathophysiology of psoriasis. Specifically, he noted that response pathways in metabolism and the immune system have a high degree of integrated regulation where insulin resistance appears to be central to the “psoriatic march.”¹ While insulin is traditionally thought of as a central agent in the metabolic system, it may also have an important role in skin homeostasis. Epidemiologic studies have shown that patients with psoriasis have a greater prevalence and incidence of diabetes compared to the general population^{2,3,4,5}. However, translational studies determining the role of insulin resistance in psoriasis and PsA pathogenesis are scarce^{6,7,8,9,10,11}.

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Dr. Boehncke discussed his group’s work showing that interleukin 1 β (IL-1 β) is present in high quantities in tissue fluid collected via microdialysis from patients with psoriasis, and that these levels can be reduced with anti-psoriatic therapy. It appears that IL-1 β induces insulin resistance through p38MAPK (mitogen-activated protein kinase), which blocks insulin-dependent differentiation of keratinocytes. Further, IL-1 β stimulates keratinocyte proliferation, which contributes to psoriasis pathogenesis and progression. This work suggests that insulin resistance acts not only as a major contributor to CV comorbidities, but that insulin resistance could also play a contributing role in the pathogenesis of psoriasis⁶.

Effect of tumor necrosis factor inhibitors on CV comorbidities

Studies have shown that patients with psoriasis and PsA have an increased prevalence of CV risk factors and greater risk for subsequent major adverse CV events including myocardial infarction (MI)^{2,5,12,13,14,15,16,17,18,19,20,21,22,23}. Because atherosclerosis is an inflammatory disease, a reduction in Th1-mediated inflammation could theoretically reduce rates of incident MI among patients with psoriasis and PsA. Therefore, whether systemic treatments for psoriasis and PsA could modify the risk of CV comorbidities is a clinically important question. The panel focused on this risk with the US Food and Drug Administration-approved tumor necrosis factor (TNF) inhibitors for the treatment of psoriasis and PsA.

We first discussed the article by Solomon, *et al* on the effect of disease-modifying antirheumatic drugs (DMARD) on the risk of developing diabetes mellitus (DM) in patients with rheumatoid arthritis (RA) and psoriasis²⁴. This retrospective cohort study included 121,280 patients and utilized

administrative data from 2 large health insurance programs (1 Canadian and 1 American). The adjusted Cox proportional hazards [hazard ratio (HR)] showed that, compared to patients prescribed nonbiologic DMARD, those prescribed TNF inhibitors (HR 0.62, 95% CI 0.42–0.91) or hydroxychloroquine (HR 0.54, 95% CI 0.36–0.80) but not methotrexate had significantly reduced risk for developing diabetes. It was noted that the patient population comprised mostly those with RA; patients with psoriasis and PsA comprised less than 10% of the overall study cohort. Therefore, the magnitude of DMARD effect on risk of DM among patients with psoriasis and PsA is not well understood and needs to be characterized with larger cohorts.

We then discussed a recently published article by Wu, *et al*²⁵. The authors conducted a retrospective study analyzing the Kaiser Permanente Southern California health plan to assess the effect of TNF inhibitor therapy on MI risk among a population of 8845 patients with psoriasis and PsA: after a median of 4.3 years of followup, patients with psoriasis treated with TNF inhibitors (adalimumab, etanercept, or infliximab) had half the risk of developing MI (HR 0.50, 95% CI 0.32–0.81) compared to those prescribed topical agents. Further, patients aged > 60 years using TNF inhibitor therapy had a greater relative reduction in MI risk (HR 0.32, 95% CI 0.14–0.73), compared to those ≤ 60 years of age (HR 0.46, 95% CI 0.25–0.88)²⁵. While these novel findings are noteworthy, it is also important to interpret these results in the context of other literature^{13,26}. Several questions were raised: Should age have been treated as a continuous variable in the adjusted model? Were interaction terms fully explored? And were methods appropriate to fully account for confounders among the different groups?

We also discussed the study by Abuabara, *et al* using US claims data, where the authors found a nonsignificant increase in MI risk in the systemic treatment group (including TNF inhibitors) compared to patients receiving ultraviolet B (UVB) phototherapy²⁶. An accompanying editorial noted that of the many reasons why CV disease risk reduction was not detected, the most common concern is whether the study design is adequate to properly test the study question²⁷. Importantly, in followup letters to the editor, the authors said that the models were also analyzed with individual treatment categories (including TNF inhibitors), and that the results did not change significantly with reference to the control UVB group; however, data were not shown. Contrary to Wu, *et al*, Abuabara, *et al* found a trend toward a cardioprotective effect for systemic treatments compared to UVB among younger patients (< 50 years), but they observed a nonsignificant trend toward an increased HR for MI risk among older patients²⁶. Although differences in study populations and design could have contributed to differences in the study findings, the panelists agreed that future studies need to incorporate direct measures of psoriasis and PsA severity and more compre-

hensive and accurate ascertainment of potential confounders. Further, a randomized controlled trial remains the gold standard for determining the effect of biologic agents such as TNF inhibitors on CV comorbidities.

Effect of IL12/23 inhibitors on CV outcomes

Interleukin 12/23 monoclonal antibody (IL12/23) inhibitors are a new class of biologics that are highly effective in the treatment of moderate to severe plaque psoriasis. Randomized trials of ustekinumab and briakinumab had a numerical excess of major adverse CV events, leading to concerns that IL12/23 inhibitors may be associated with adverse CV outcomes^{28,29}. Longterm data on ustekinumab, however, has suggested a profile of overall safety of this agent without definitive evidence of CV harm or benefit³⁰.

We discussed 2 recent metaanalyses that sought to address the effect of IL12/23 inhibitors on CV outcomes. The first metaanalysis included all double-blind placebo-controlled trials of ustekinumab and briakinumab³¹. Using a fixed-effects model and risk difference as the primary outcome measure, the authors found a risk difference of 0.012 events/person-year among patients randomized to IL12/23 inhibitors, with a 95% CI range of 0.001 to 0.026 events/person-year. The second metaanalysis used the same clinical trial data but found that IL12/23 inhibitors were associated with statistically significant higher odds of major adverse CV events (OR 4.23, 95% CI 1.07–16.75)³².

In discussing these 2 metaanalyses, several issues were raised. The first metaanalysis did not find any statistically significant association between IL12/23 inhibitors and major adverse CV events, but the 95% CI included a wide enough margin that larger-scale phase IV studies are still necessary to identify any association between these agents and a population-attributable risk of adverse outcomes. The second metaanalysis utilized an alternative methodology known as the Peto method, which is unstable in situations of low event rates. Because 5 of the trials did not have any events in either the placebo group or the treatment group, those 5 trials were actually excluded from the pooled metaanalysis estimate. This second metaanalysis may therefore have significant flaws that limit any interpretation. Moreover, neither analysis controlled for duration of followup, which tends to introduce bias as more patients drop out of the placebo group compared to the treatment group and thus could result in spurious safety signals³³.

We then discussed conflicting data regarding the role of IL-17 in atherosclerosis. Mechanistic investigations have yielded conflicting results, with some studies suggesting that IL-17 is associated with increased atherosclerosis, while others have suggested that IL-17 stabilizes coronary artery plaques^{34,35}. More research is needed in this area to better understand the underlying biology of IL-17. Also discussed was the observation that the CV events in the

randomized trial of briakinumab all occurred in patients with multiple CV risk factors²⁸. These findings emphasize the importance of screening patients with psoriasis for CV disease, and that patients with moderate to severe psoriasis have a higher prevalence of CV risk factors compared to the general population.

Future research directions in CV comorbidities of psoriasis and psoriatic arthritis

The number of epidemiologic, translational, and basic studies on the topic of CV comorbidities of psoriasis and PsA has continued to increase during the past 5 years. The wealth of epidemiologic data from various populations around the world will need to be matched with basic and translational efforts to determine the mechanisms underlying these epidemiologic findings.

The panelists identified several important research directions regarding both study questions and study designs. First, epidemiologic studies need to focus on large, sufficiently powered cohorts, to determine whether a relationship truly exists between the factors of interest. Small studies with a limited number of participants can be informative when an association is identified; however, when no a priori specified associations are identified, it remains difficult to determine whether this finding is attributable to a true absence of relationship or insufficient power. Second, investigators will need to devise systematic methods for capturing psoriasis and PsA disease severity to separate the effect of the disease from that of medications. Third, to determine the precise effect of biologic therapy on CV comorbidities, a large randomized controlled trial would control for known and unknown confounders; its findings would be highly valuable to the psoriasis community. In the interim, rigorous randomized controlled trials that evaluate the effects of psoriasis treatment on biomarkers of CV risk, such as vascular inflammation, will be important for further defining the impact of treating psoriasis beyond the skin³⁶. Fourth, efforts are necessary to determine if patients with moderate to severe psoriasis should be targeted for more intense goals for lipid control, as has been recommended for RA^{37,38,39}.

Finally, increased efforts in basic and translational investigations are needed to determine the shared mechanisms between psoriatic diseases and CV comorbidities and to advance the development of new therapeutic targets.

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