Recent Highlights in Psoriasis Research

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This article highlights recent advances in the immunology, epidemiology, and genetics/genomics of psoriasis from 2015 through 2016. Advances sometimes generate more questions, and this article makes an attempt to point out where controversies might exist in the literature. Many of the articles mentioned were published in the Journal of Investigative Dermatology, but many articles from the broader scientific literature are also cited, to provide context and to add further validity for some of these key findings. Among the themes we explore are the identification of antigens in psoriasis, the co-morbidities of psoriasis, and novel integrative approaches to genome-wide association studies.

Journal of Investigative Dermatology (2016) ■, ■–■; doi:10.1016/j.jid.2016.11.007

INTRODUCTION

Advances in psoriasis research continue unabated, even as biologics have revolutionized the way many patients with moderate to severe disease are treated. In this article, we highlight specific advances and findings in psoriasis research related to epidemiology/clinical research, immunology, and genetics. Many of these studies were published in the *Journal of Investigative Dermatology* (*JID*), but others help put these studies in context. Tamar Nijsten focuses on novel, but contradictory, epidemiological data regarding what was thought to be a known comorbidity of psoriasis, as well as on new biomarkers that might improve or "personalize" the way we give therapy in psoriasis. Samuel T. Hwang highlights advances in the role of antimicrobial peptides in terms of how they are regulated and how they might act as antigens in psoriasis and explores the role of skin inflammation as it relates to alterations in adipocyte biology. James T. Elder highlights genetic and genomic advances contributing to our understanding of psoriasis, including novel integrative approaches to genome-wide association studies, bioinformatic tools for transcriptomic comparison of psoriasis versus other skin diseases, and exploration of the contribution of long noncoding RNAs (lncRNAs) to psoriasis pathogenesis.

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Abbreviations: CVD, cardiovascular disease; GWAS, genome-wide association study; hBD2, human β-defensin 2; JID, Journal of Investigative Dermatology; lncRNA, long noncoding RNA; miR, microRNA; TNF-α, tumor necrosis factor-α

Received 1 November 2016; accepted 2 November 2016; corrected proof published online XXX

EPIDEMIOLOGY AND CLINICAL RESEARCH

Cardiovascular comorbidities

Since the 2006 landmark study by Gelfand et al. (2006), many, but not all, studies have shown a positive association between metabolic syndrome and cardiovascular disease (CVD) and psoriasis, especially for (young) patients with moderate to severe disease (Armstrong et al., 2013; Gelfand et al., 2006). Most of the observational studies suffered from residual confounding and were not able to assess psoriasis severity, challenging the causality of the observed observation (Nijsten and Wakkee, 2009). The main hypotheses are that the enhanced systemic inflammatory status of psoriasis patients increased their risk or that they share a genetic predisposition to develop these comorbidities. Almost 10 years after Gelfand et al.'s study, the Clinical Practice Research Datalink was reanalyzed by the Manchester team, changing some of the previous assumptions and applied methodology (i.e., incident versus prevalent CVD, varying time of disease severity, including psoriatic arthritis as a covariate, and reclassifying some patients' disease severity on the basis of drug exposure) (Parisi et al., 2015). They confirmed the higher prevalence of CVD risk factors in psoriasis patients but, interestingly, did not find an overall higher risk of myocardial infarction. They concluded that, based on the Clinical Practice Research Datalink data, "Neither psoriasis nor severe psoriasis were associated with the short term risk of major CV events after adjusting for known cardiovascular risk factors" (p. 2189).

In 2015, a German cross-sectional study of 4,185 psoriasis patients showed that severe psoriasis patients were at a slightly increased risk for incident diabetes and myocardial infarction (adjusted relative risk < 1.15) (Koch et al., 2015). The uniqueness of this study was that these researchers were the first to compare the genetic architectures in 927 psoriasis patients with almost 4,000 controls. They used the Metabochip (Illumnia Inc., San Diego, CA) custom array to densely genotype and analyze established coronary artery disease risk loci (nearly 200,000 single nucleotide polymorphism markers) showing that only two single nucleotide polymorphisms associated with coronary artery disease were associated with psoriasis and that none of the psoriasis single nucleotide polymorphisms were associated with coronary artery disease. They concluded that "the genetic architecture of psoriasis and cardiometabolic traits is largely distinct" (p. 1283).

A recent 2016 study in *Circulation Research* showed that GlycA, which is a novel biomarker for systemic inflammation, was associated with psoriasis severity and subclinical CVD in a cross-sectional study in two cohorts (Joshi et al., 2016). Altogether, the two cohorts included more than 300 psoriasis patients, and in one of the cohorts (151 psoriasis

patients and 30 control subjects) the subclinical CVD was assessed by VI by 18-fludeoxyglucose positron emission tomography/computed tomography scan and coronary CT angiography. GlycA was significantly, but modestly, correlated with several inflammatory cytokines (correlation coefficients between 0.73 and 0.12) and cardiometabolic traits (correlation coefficients varied mostly between 0.20 and 0.40). Adding GlycA to the base model that included conventional CVD risk variables further increased the area under the receiver operating characteristic curve for VI from 0.86 to 0.93 and for coronary artery disease from 0.89 to 0.92, suggesting that this biomarker added some value in predicting subclinical CVD in psoriasis patients. Altogether, this comprehensive study suggests that at a subclinical CVD level, psoriasis patients differ from control subjects.

Access to care and drug survival

Although the management of psoriasis has changed dramatically with the introduction of multiple biologics and a new oral drug, relatively little was known about the level of access to care in different countries. In the US Medicare population, it was estimated that approximately 1% of the elderly had sought care for their psoriasis (Takeshita et al., 2015). Of the total Medicare psoriasis sample, about a quarter had used phototherapy or oral systemic or biologic therapies; of these, 37.2% had used biologics (10.1% of total psoriasis sample). Elderly black psoriasis patients and those without a low-income subsidy were 70% less likely to have received biologics for their psoriasis. Patients living in an urban county with higher levels of dermatology and primary care provider density, as well as those with concomitant inflammatory conditions, were more likely to have used biologics. In a follow-up study in the same population, it was shown that about 80% of patients used adalimumab or etanercept and that both infliximab and ustekinumab were used in approximately 10% of patients between 2009 and 2012. In the 12 months after having started an antipsoriatic biologic, 38% of patients using biologics were adherent, 46% discontinued, 8% switched, and 9% restarted the therapy (Doshi et al., 2016). Female patients and those without a low-income subsidy were at increased odds of decreased adherence.

The use pattern of biologics in the UK differed from the United States in that adalimumab (56.2%) was more commonly used, followed by etanercept (33.4%) and ustekinumab (10.4%) in a national registry of predominantly biologic-naïve patients between 2007 and 2014 (Iskandar et al., 2016). In a 12-month period, 77.4% of the 2,980 UK patients continued the biologic, and more than 85% used the recommended dose. However, a quarter of patients combined conventional drugs, which was most often methotrexate, with the biologic it was initiated on. Although there are clear distinctions with respect to data source and study population between the US and UK in the study, there seem to be real geographic differences in real-world care of psoriasis. The same research group investigated drug survival of biologic therapies in the prospective UK registry. Among 3,523 patients, the overall drug survival rate in the first year was 77%, falling to 53% in the third year. Compared with adalimumab users, patients on etanercept and infliximab were 60% more likely to discontinue therapy, and those on ustekinumab were 50% more likely to continue therapy. In contrast with the US Medicare study, this study had more detailed patient information to assess risk factors associated with discontinuation and showed that female sex, current smoker, and higher quality-of-life impairment were predictors of stopping treatment, whereas the presence of psoriatic arthritis increased the likelihood of continuation by 60% (hazard ratio = 1.63, 95% confidence interval = 1.45−1.84).

Advances in personalized medicine for psoriatic patients

The abovementioned observational studies investigating the predictors of drug survival are small steps toward the highly desirable concept of personalized medicine. Another approach toward personalized treatment is measuring trough levels of the biologics, which might also explain why more obese patients seem to respond less to biologics (Zweegers et al., 2016). A Dutch and Belgian research group estimated a therapeutic range of adalimumab trough levels between 3.5 and 7.0 mg/L to be associated with a more optimal clinical effect (Menting et al., 2015a). They also suggested that about a third of psoriasis patients using adalimumab exceeded the therapeutic window, allowing a rationale for extending the treatment intervals. However, the diagnostic properties (sensitivity and specificity were less than 80%) of the therapeutic range require improvement, and the concept should be validated in a larger prospective psoriasis cohort. The same research group observed no correlation between trough levels of ustekinumab and treatment response (Menting et al., 2015b).

In 2016, an interesting large pharmacogenetics study was published using well-defined psoriasis patients taking ustekinumab derived from three randomized clinical trials (Li et al., 2016). The HLA-C*06:02 allele is known to substantially increase the risk of psoriasis and is associated with earlier onset and more severe disease. The overall HLA-C*06:02 prevalence was 44.6% in the psoriasis cohort. Both the HLA-C*06:02-positive and -negative psoriasis patients responded well to ustekinumab (86% and 76%, respectively, achieved 75% reduction in psoriasis area severity index at week 24). According to different sensitivity analyses, a possible modest differential response to ustekinumab in HLA-C*06:02-positive patients achieving higher response rates for getting (almost) clear at later time points was shown. Although the effect of HLA-C*06:02 is limited, the robust assessment of pharmacogenetic biomarkers is definitely the way forward to optimize care in the most cost-effective manner.

PSORIASIS IMMUNOLOGY

Antimicrobial peptides in psoriasis: from passive bystanders to active antigens

Antimicrobial peptides, including the β-defensins and LL-37, have long been known to be overexpressed in psoriatic lesions. Given the known antibacterial properties of most of these small proteins, this might explain the relatively low presence of bacterial and bacterial infections in psoriatic lesions. But what roles, if any, do these highly conserved small proteins play in psoriasis pathogenesis? The recent publications described below provide new insights into the complex regulatory mechanisms that regulate their