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Psoriasis Therapy: Breakthroughs in Pharmacogenomics or in Pharmacology?

Mark Lebwohl[1]

As the cost of psoriasis therapies skyrockets, it becomes increasingly important to find biomarkers that predict which patients will respond to expensive medications. The ability to predict response to a specific therapy is particularly important for medications that are effective in only a small portion of the population. As we develop medications that clear most patients, the need for a predictive biomarker diminishes. Nevertheless, the importance of pharmacogenomics is likely to increase as the cost of drugs continues to rise.

Journal of Investigative Dermatology (2016) **136,** 2339–2340. doi:10.1016/j.jid.2016.07.019

Li et al. (2016) have published an intriguing study that suggests that the presence of HLA-CW6 allele may predict patients who will respond better to ustekinumab therapy. In the pivotal studies of ustekinumab, 86% of HLA-C*06:02 positive patients achieved psoriasis area and severity index (PASI) 75 compared with 76% of HLA-C*06:02 negative patients at week 24. Looking at multiple end points and time points, the authors were able to identify the largest difference in PASI 75 at week 12 (17.9% more HLA-C*06:02 positive patients achieved that end point than negative patients). There was an 11.8% difference in PASI 90 end points at week 24 and a 10.2% difference in PASI 100 at week 28 favoring the allele-positive patients compared with the negative patients. The authors correctly point out that these differences are modest.

The first biologic approved for psoriasis was alefacept. In the pivotal trials for that drug, only 33% of patients achieved PASI 75 at any point during the trial. Moreover, the drug had to be administered by intramuscular injection in the physician's office for 12 consecutive weeks, and the peak response did not occur until several weeks later (Lebwohl et al., 2003). A biomarker to predict which patients would achieve PASI 75 would certainly have been helpful for that drug. In patients who responded to alefacept and were then treated with repeated courses, response rates on retreatment of responders were higher, suggesting that responders might be a genetically distinct group that could be identified (Goffe et al., 2005). Unfortunately, no genetic differences, biomarkers, or phenotypic differences were ever identified that could predict response to alefacept.

> In an era of personalized medicine, the ability to identify genetic markers that predict response to medications is certainly valuable, but the value is clearly greatest when the overall response rate is low.

Although biomarkers would certainly have been valuable for older therapies that did not perform as well, the need for biomarkers diminishes as the drugs approved for psoriasis achieve consistently better results. Between 70 and 80% of patients achieved PASI 75 with ustekinumab, and even higher numbers of patients achieved PASI 75 with our newest drugs, secukinumab, ixekizumab, and brodalumab. For the latter drugs, simply having plaque psoriasis predicts response to IL-17 blockade in more than 80% of patients.

Will we need biomarkers to identify PASI 90 or PASI 100 responders with some of these new drugs? Although an inexpensive, reliable, biomarker would certainly be welcome before starting patients on very expensive medications, such a test would have to add value by predicting improvements in quality of life before starting on expensive therapies. If major improvements in quality

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of life occur in achieving PASI 75, will insurers pay for expensive drugs just to get to PASI 90 or PASI 100, even if those levels of improvement have been associated with greater quality of life improvements?

And, are there other factors, such as environmental factors or phenotypic factors, that should be considered along with biomarkers to predict responders? For example, are obese patients more or less likely to respond? Trials with most drugs would suggest that low body weight improves the likelihood of response.

In an era of personalized medicine, the ability to identify genetic markers that predict response to medications is certainly valuable, but the value might be even greater for drugs that do not achieve such high response rates. Acitretin, methotrexate, and apremilast, for example, require months of treatment before achieving optimal benefit, and the proportion of PASI 75 responders in those three groups is less than 50%. A biomarker to predict response to any of those drugs would certainly be welcome.

As the treatment options for psoriasis increase, the availability of biomarkers would certainly be welcome, but we all hope to see the day when we have a completely safe medication that allows 100% of patients to achieve PASI 100. At that point, we will not need a genetic marker to predict response.

CONFLICT OF INTEREST

ML is an employee of the Mount Sinai Medical Center that receives research funds from AbGenomics, Amgen, Anacor, Boehringer Ingleheim, Celgene, Ferndale, Lilly, Janssen Biotech, Kadmon, LEO Pharmaceuticals, Medimmune, Novartis, Pfizer, Sun Pharmaceuticals, and Valeant.

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Atopic Dermatitis According to GARP: New Mechanistic Insights in Disease Pathogenesis

Janna Nousbeck[1,2] and Alan D. Irvine[1,2,3]

In complex disease such as atopic dermatitis, the journey from identification of strong risk loci to profound functional and mechanistic insights can take several years. Here, Manz et al. have elegantly deciphered the mechanistic pathways in the well-established 11q13.5 atopic dermatitis risk locus. Their genetic and functional insights emphasize a role for T regulatory cells in atopic dermatitis pathogenesis.

Journal of Investigative Dermatology (2016) **136,** 2340–2341. doi:10.1016/j.jid.2016.08.020

The etiology of atopic dermatitis (AD) is multifactorial. It includes interactions between environmental and genetic factors that lead to skin barrier dysruption and both cutaneous and systemic immunologic dysfunction (Weidinger and Novak, 2016). Although null mutations in *FLG*, encoding an epidermal barrier protein, are the strongest and best replicated genetic risk factors for AD, these mutations are present in only up to 50% of patients (Irvine et al., 2011), meaning that identification and deeper understanding of other genetic risks involved in this complex trait are required. To date, genome-wide association studies have identified more than 30 loci associated with AD risk (Paternoster et al., 2015). These loci include candidate genes harboring roles in innate and acquired immune responses, emphasizing the importance of immune responses in AD. Of these 31 loci, *FLG* on Chr1q21 is the only locus for which a significant body of functional and genotype/phenotype correlative data has been generated (McAleer and Irvine, 2013). One susceptibility region, on chromosome 11q13.5, was reported initially in 2009 (Esparza-Gordillo et al., 2009), and it has been replicated as an AD risk locus in several subsequent studies (O'Regan et al., 2010, Paternoster et al., 2015). It has also been associated with other allergic and inflammatory diseases (Barrett et al., 2008; Marenholz et al., 2015); however, the functional role of variants in this locus in AD pathogenesis was unknown. Manz et al. (2016) report genetic association and functional data that reveal an important role for glycoprotein A repetitions predominant (GARP) in the pathogenesis of AD.

> In this elegant study, Manz et al. further our understanding of the pathogenesis of atopic dermatitis by demonstrating the functional importance of variations in *LRRC32* on the well-established 11q13.5 atopic dermatitis risk locus.

Using a targeted next-generation sequencing of the 11q13.5 locus in

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