treated with topical calcipotriol plus 5-fluorouracil immunotherapy suggest that group 1 ILCs may play a key role in cSCC immunoprevention (Cunningham et al., 2017). Accordingly, a comprehensive examination of ILCs in human precancerous skin lesions is warranted to gain fundamental insights into how keratinocytes early malignant transformation is regulated by ILCs to enable optimal immunotherapeutic approaches to prevent cSCC development.

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CONFLICT OF INTEREST
The authors state conflict of interest.

REFERENCES


Patients with psoriasis and psoriatic arthritis are at an increased risk of cardiovascular (CV) events. A recent systematic review and meta-analysis by González Cantero et al. (2021) evaluated the effects of biologics on CV imaging and biomarkers in patients with psoriasis. In this commentary, we discuss the clinical and management implications of these and the related results for patients with psoriatic disease and the need for further pharmacoepidemiological research. Journal of Investigative Dermatology (2021) 141, 2322–2325. doi:10.1016/j.jid.2021.04.012

In common with many chronic inflammatory diseases, psoriasis and psoriatic arthritis (PsA), often referred together as psoriatic disease, are associated with increased risk of cardiovascular (CV) events and mortality, even when traditional CV risk factors are taken into account. The extent of this excess risk remains uncertain, but it is estimated to be around 50%, and it may be greater in those with younger age of onset (Ferguson et al., 2019).

Over the past two decades, there have been significant advances in the understanding and management of psoriatic disease, with the development of effective biologic therapies targeting the proinflammatory TNF and IL-23/IL-17 pathways. The phase 2 and 3 studies of these biologics focus on psoriatic disease activity as primary outcome and safety and patient-reported outcomes as secondary outcomes, but CV risk has not been well-studied. In the Journal of Investigative Dermatology, González Cantero et al. (2021) present a systematic literature review (SLR) and meta-analysis of the impact of biologic agents on imaging and laboratory biomarkers of CV disease (CVD) in patients with psoriasis. The SLR included results from five placebo-controlled trials (n = 489) and meta-analysis from only two trials (n = 87), with no significant beneficial effect identified on CV imaging biomarkers (aortic vascular inflammation or flow-mediated dilatation) with adalimumab or secukinumab. A reduction in aortic vascular inflammation was reported with ustekinumab at 12 weeks but not at 52 weeks after the open-label

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Estimating Cardiovascular Impacts of Drugs for Psoriatic Disease: A Long Way to Go
Stefan Siebert1 and Naveed Sattar2

Patients with psoriasis and psoriatic arthritis are at an increased risk of cardiovascular (CV) events. A recent systematic review and meta-analysis by González Cantero et al. (2021) evaluated the effects of biologics on CV imaging and biomarkers in patients with psoriasis. In this commentary, we discuss the clinical and management implications of these and the related results for patients with psoriatic disease and the need for further pharmacoepidemiological research. Journal of Investigative Dermatology (2021) 141, 2322–2325. doi:10.1016/j.jid.2021.04.012

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Clinical Implications

- There is limited evidence regarding the impact of biologic therapies on cardiovascular (CV) outcomes in psoriasis.
- Pharmacoepidemiological research programs with robust methodology are required to estimate CV impacts of therapies.
- Management should focus on controlling both inflammatory disease and cardiometabolic risk factors.

Understanding CV risk and the impact of therapies on CV risk in patients with psoriatic disease

While the underlying mechanisms of increased CV risk in psoriatic disease are multifactorial, overwhelming evidence indicates that higher-grade systemic inflammation plays a major contributory role in chronic inflammatory conditions such as rheumatoid arthritis (RA) and PsA (Ferguson et al., 2017). This is consistent with the wider literature indicating that increased CV risk in the general population is associated with CRP levels (Emerging Risk Factors Collaboration et al., 2010). Furthermore, there is accumulating evidence that reducing inflammation in groups at elevated CV risk leads to fewer CV events. In the large Canakinumab Anti-Inflammatory Thrombosis Outcome Study randomized controlled trial, IL-1β inhibition with canakinumab in patients with a previous history of myocardial infarction significantly reduced major CV events, which correlated with the magnitude of the reduction in high-sensitivity CRP but was independent of lipid changes (Ridker et al., 2017). It is not possible or ethical to do long-term placebo-controlled studies in patients with chronic inflammatory conditions who require regular active therapy for their underlying inflammatory condition, so other methods are required to estimate the likely effects of biologic and other immunomodulatory therapies on CV outcomes in these conditions. In the absence of randomized controlled trials, there are two main options, namely surrogate markers and long-term observational studies.

Assessments of surrogate markers of CV events are commonly proposed to gauge the impact of therapies on difficult to study longer-term CV outcomes. Although this approach is appealing, considering the more rapid outcomes and smaller numbers required, it is dependent on a close correlation between the changes in these surrogate markers and the reduction in CV events in that population. Similarly, although aortic inflammation is an appealing surrogate measure, there are simply too little prospective data to consider this a robust marker to estimate changes in future CV outcome risk. The same is true for all current vascular function measures, none of which are recommended for use in routine clinical practice.

The majority of the serum CV biomarkers included in the SLR by González Cantero et al. (2021) are inflammatory markers associated with psoriasis itself. Interestingly, CRP is not typically reported in phase 3 studies of biologics in patients with psoriasis, in contrast to PsA where CRP is often both an inclusion criterion and part of composite outcomes (although not necessarily reported as an outcome in isolation). Post hoc analyses and other studies indicate consistent reductions in CRP with effective biologics, including the inhibitors of TNF and the IL-23/IL-17 pathway, in psoriatic disease, suggesting that these agents do reduce this surrogate CV biomarker despite the limited evidence in the specific CV studies included in this SLR. There is some circularity because these therapies reduce inflammation in psoriasis, so their effect on CV inflammatory biomarkers should only be expected in those patients who respond to that therapy. Furthermore, the elevation in low-density lipoprotein cholesterol seen with some therapies—as shown in this SLR—cannot be ignored, and the systematic assessment of the effects of these therapies on many other CV risk factors or indeed body composition are generally lacking. Thus, one cannot infer a reduction in CV risk simply by pointing to expected changes in inflammatory markers. Much more nuance and detail are needed.

In contrast, observational studies are by nature bedeviled by potential confounding and bias, particularly confounding by indication where patients at the highest risk of a particular outcome (namely those with highest disease activity) are more likely to receive treatment with a specific therapy such as a biologic agent. A relevant example of this is seen in a commonly cited paper, which reported that the rates of myocardial infarction were similar between patients with RA who received a TNF inhibitor and those who received conventional synthetic disease-modifying antirheumatic drugs, whereas the rate was 64% lower in patients whose RA disease activity responded to TNF inhibitors than in nonresponders, suggesting but not proving that reduction of disease activity may be key to a potential reduction in the risk for CVD in these patients (Dixon et al., 2007). Subsequent meta-analyses of observational data have further suggested that lower CVD risk may stem from the use of TNF inhibitors and methotrexate in patients with RA (Roubille et al., 2015). However, such data for patients with psoriatic disease were limited, and it should be noted that pharmacoepidemiological methods to lessen confounding and bias have since improved so that reanalysis of many previous observational studies in this area may be merited.

Although reducing inflammation is likely to lower CVD risk, it should not be assumed that all immunomodulatory agents will have the same effects on CV outcomes, as demonstrated by corticosteroids, which effectively and rapidly reduce inflammation but are associated with higher CV risk, particularly in higher systemic doses, likely in part owing to adverse effects on blood pressure and glycemia (Hippisley-Cox et al., 2017). Although data for
biologics other than TNF inhibitors are more limited and mixed, it is now largely accepted in RA, where biologics have been used for longer and an early aggressive treat-to-target therapy has been established in routine clinical practice, that improved control of inflammation, regardless of whether with biologic or methotrexate, likely contributes to the lessening of CV risk (Ferguson et al., 2019). This impression is indirectly shown by the large TkiAil of Atorvastatin for the primary prevention of Cardiovascular Events in patients with RA placebo-controlled randomized controlled trial of statins for the prevention of CV events in RA, which had to be prematurely terminated owing to a far lower-than-expected current CV event rate compared with calculations based on historic data (Kitas et al., 2019).

Psoriatic disease and its management are more heterogeneous than RA and its management, with many patients requiring only topical or limited therapy, making within-disease comparisons more complex and liable to confounding. Whereas the observational data for the effects of biologic therapies on CV outcomes in psoriasis and PsA are still more limited than in RA, the initial emerging data suggest concordant associations. However, it cannot simply be assumed that such effects will be the same in all chronic inflammatory conditions. RA is characterized by significantly more systemic inflammation than either PsA or psoriasis, so changes in inflammation with immunomodulatory therapy are likely to be more marked in RA. Furthermore, comorbidities differ between these conditions, with higher levels of obesity and diabetes mellitus—both established causal risk factors for CV—more strongly associated with psoriatic disease than with RA (Ferguson et al., 2019; Jafri et al., 2017).

Implications of the SLR and related findings for clinicians treating patients with psoriatic disease
At this stage, neither current novel imaging nor serum surrogate marker data in psoriatic disease are sufficient to confirm or refute the CV benefit of the tested therapies. Even so, a clear priority in clinical practice should be good control of inflammatory disease using effective therapies while minimizing the use of therapies, most notably systemic corticosteroids, which can potentially worsen CV outcomes. The likelihood is that CV risk is lessened by this process, but whether remission (or complete skin clearance) is required or can reduce CV events to general population levels requires further detailed analyses.

These sobering thoughts remind us that all clinicians must be aware of the increased CV risk associated with psoriatic disease and actively discuss this with their patients. This process should include early calculation of CV risk—easily done by adding nonfasting lipids to routine monitoring blood tests and taking systolic blood pressure measurements—and then appropriate prescription of statins or antihypertensives in those at elevated risk (Sattar et al., 2020). Furthermore, because more patients with psoriatic disease are overweight or have type-2 diabetes, these two risk factors also merit attention. Fortunately, there are now better methods to help our patients make sustainable lifestyle changes to stop smoking and lose weight as well as better treatments for diabetes that aid weight loss and lessen CV risk, as recently reviewed (Sattar et al., 2020; Taylor et al., 2021). Dermatologists and rheumatologists managing patients with psoriatic disease would do well to assimilate some of this knowledge because even small intentional or drug-related improvements in weight trajectory could have important benefits for patients. As such, the mantra must be multidisciplinary and holistic management to help our patients gain the best care. It is no longer sufficient to simply assess skin (and joints in the case of PsA) disease activity.

Improving evidence on the impact of therapies on CV risk changes in psoriatic disease
As the number of effective therapies available to control active skin psoriasis and, to a lesser extent, inflammatory musculoskeletal disease in PsA continues to grow, the focus will increasingly shift to their longer-term and potential CV impacts. Clearly, substantially more evidence to estimate the likely effects of specific biologic agents on CV risk is required, particularly with the advent of small-molecule inhibitors, which may have very different cardiometabolic profiles and effects from the current anticytokine therapies. At this stage, the evidence in the SLR and other studies does not inform the choice of biologic based on CV benefit. In the absence of the ability to perform placebo-controlled trials, carefully designed cohort studies, in both early and established disease, with long-term CV outcomes will be required. These should be part of large coordinated pharmacoepidemiological programs, incorporating active comparators and utilizing new-user design (to prevent immortal time bias) and other specific methodological strategies to lessen selection and other biases (D’Andrea et al., 2021). As more electronic healthcare data become available, such studies should soon be a reality in psoriatic disease. Furthermore, CV outcomes should be included as standard measures in phase 3 trials as well as utilizing routine-data linkage for capturing relevant long-term CV outcomes in these trials. Similarly, trials should be encouraged to collect and biobank samples so that collaborative groups could take advantage of the novel omics technologies to better estimate changes in CV risk in the future.

In conclusion, biologics and other therapies offer a potential opportunity to impact CV risk in psoriatic disease, but current surrogate marker and observational research are too limited to be certain about such benefits. Presently, therefore, clinicians should focus on both good control of active inflammatory disease and more comprehensive management of cardiometabolic risk factors, particularly those that commonly accompany psoriatic disease.

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CONFLICT OF INTEREST
SS has received honoraria for advisory boards from AbbVie and Janssen Pharmaceutica and speaker fees from AbbVie, Biogen, Celgene, Janssen Pharmaceutica, and Novartis, outside the submitted work. NS reports receiving research grant and personal fees from Boehringer Ingelheim and personal fees from Amgen, AstraZeneca, Eli Lilly, Merck Sharp & Dohme, Novartis, Novo Nordisk, Pfizer, and Sanofi, outside the submitted work.
Fanning the Flames: IRAK2 Signaling in Differentiated Epithelium Potentiates Skin Inflammation

Rochelle Castillo1,5, Ipsita Subudhi2,5 and Shruti Naik1,2,3,4

Aberrant epidermal differentiation is a hallmark of inflammatory skin diseases, including psoriasis and atopic dermatitis. If and how differentiated epidermal cells contribute to inflammatory pathology is unclear. In their new article in the Journal of Investigative Dermatology, Shao et al. (2021) report that IRAK2 signaling downstream of IL-1 and IL-36 links epidermal differentiation and skin inflammation.


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Psoriasis and atopic dermatitis (AD) are two clinically, histopathologically, and immunologically distinct chronic skin diseases that are typified by immune hyperactivation and epidermal dysfunction (Guttman-Yassky et al., 2011). The characterization and targeting of different lymphocyte subsets and their corresponding inflammatory mediators have revolutionized the treatment of both psoriasis and AD. What is less clear is how different epidermal cell populations sense and respond to inflammatory signals. Shao et al. (2021) had previously found that the production of the IL-36 group of cytokines correlates with inflammatory disease severity (Johnston et al., 2011). In addition, the ability of IL-36 cytokines to modulate both immune and epithelial components prompted an exploration of how these factors may link the epidermal differentiation and inflammation circuitry.

In their new article in the Journal of Investigative Dermatology, Shao et al. (2021) identify IRAK2 signaling in differentiated epithelia as essential for both epidermal hyperdifferentiation and potentiation of inflammation. By elegantly linking clinical correlates of IRAK2 expression and inflammatory disease severity with functional studies in mouse models of psoriasis and AD, they uncover IRAK2-mediated expression of epidermal differentiation factors ZNF750 and GRHL as well as inflammatory factors IL36G, CCL20, and DEFB4, thus revealing IRAK2 as an attractive target for treating inflammatory skin disease (Figure 1).

IRAKs are central to signal transduction in the IL-36 and, more broadly, the IL-1 superfAMILY pathway (Wesch et al., 1997). How the IRAK family members IRAK1, IRAK2, IRAK3, and IRAK4 contribute to psoriatic and atopic skin inflammation was previously unclear. To address this, Shao et al. (2021) evaluated IRAK expression in the diseased epidermis of affected patients and noted significant elevation of IRAK2 in the epidermis of patients with psoriasis and, to a lesser extent, in that of patients with AD. In addition, IRAK2 levels positively correlated with disease severity as assessed by PASI and SCORing Atopic Dermatitis. To determine whether IRAK expression is modulated by...