

# Understanding Therapeutic Pathways and Comorbidities in Psoriasis

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## ■ Abstract

Psoriasis is now recognized as an immunologically mediated systemic disease that may be expressed in cutaneous and joint symptoms. Medications that were once thought to control psoriasis by reducing keratinocyte proliferation are now known to act on immunologic pathways. In recent years, the emerging understanding of immunologic pathways in psoriasis has resulted in the use of biologic medications (eg, inhibitors of tumor necrosis factor) to treat psoriasis. More recently, other pathophysiologic pathways have been identified that have the potential to expand the therapeutic armamentarium. Other avenues of research within the past decade have demonstrated that a range of health risks and comorbid inflammatory diseases are associated with psoriasis, and they have the potential to increase morbidity and mortality and adversely affect quality of life.

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## ■ Keywords

Immune-mediated inflammatory diseases; interleukin cytokine families; psoriasis comorbidities; psoriasis pathophysiology; TNF; tumor necrosis factor inhibitors

Until relatively recently, psoriasis was seen by many clinicians only as a cutaneous disease. Studies in pathophysiology identified the associated keratinocyte maturation abnormality, rapid proliferation of cells resulting in skin thickening, and vascular dilatation that explained erythema. Until the late 1980s, psoriasis generally was thought of as a hyperproliferative skin disease, and treatments—including ultraviolet B and psoralen with ultraviolet A phototherapy, methotrexate, and retinoids—were thought to result in symptomatic improvement by mitigating keratinocyte hyperproliferation.

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## The Science of Psoriasis Therapy

Clinical observation led to the earliest clues that psoriasis was immunologically mediated. It was noted that patients with psoriasis who were given cyclosporine following renal transplant surgery experienced an improvement in their skin disease. Although cyclosporine was known to be a potent immunosuppressant, further study was needed to clarify the role of the immune system in psoriasis.

An early breakthrough in the development of a model for the immunologic basis of psoriasis came with the work of Wronce-Smith and Nickoloff,<sup>1</sup> who demonstrated that psoriasis is, fundamentally, an immune-mediated inflammatory disease. In a landmark study, these researchers harvested full-thickness human skin samples from healthy volunteers and from noninvolved areas on patients with psoriasis. These samples were grafted onto severe combined immunodeficient mice, and activated autologous CD4+ T lymphocytes from the patients with psoriasis were injected into the dermis of the graft. These skin grafts from the patients with psoriasis then developed into psoriatic plaques, proving that the disease can be driven by activated circulating lymphocytes.

At the same time, new understanding of traditional medications raised questions about how they affected psoriasis. For example, as mentioned above, it was thought that the effect of treatments such as methotrexate in psoriasis was chiefly antiproliferative, working by blocking the folic acid pathway. However, studies of the impact of methotrexate on inflammation showed that methotrexate increases the levels of extracellular adenosine, an endogenous anti-inflammatory molecule.<sup>2</sup> Thus, even a medication that was traditionally considered to be antiproliferative for keratinocytes seemed to work through immunologic mechanisms.

Unfortunately, with all these studies, one element of understanding was missing: There was no clear understanding of the connection between the immune system and the skin-based abnormalities that result in the clinical findings of psoriasis. Sano et al<sup>3</sup> supplied part of the missing puzzle piece when they published the results of a study that has changed the understanding about T-cell and lymphocyte pathways in psoriasis. (Subsequently, this and other studies have led to the development of some agents currently in the research pipeline.) These researchers were attempting to create an animal model for squamous cell carcinoma (SCC) by introducing a signal transducer and activator of transcription 3 (STAT3) signal transduction molecule into skin cells and maintaining the molecule's activation. Rather than SCC lesions, however, the effort resulted in changes that resembled psoriasis plaques. Specifically, cytokines that were known to affect STAT3 activation—most importantly, interleukin 23 (IL-23)—seemed to play a critical role in psoriasis. It became evident that the IL-23 pathway

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could be the connection between the immune system and keratinocyte behavior. At the same time, some investigators were working on the development of biologic agents meant to block IL-12, based on the understanding that IL-12-driven T cells might be important in psoriasis pathogenesis. However, it later became apparent that only antibodies that blocked a specific subunit side of the IL-12 molecule—the p40 side subunit—had any effect.<sup>4</sup>

The observation was then made that IL-23 also has the same p40 subunit, and IL-23 was found to be highly overexpressed in psoriasis. Sa and colleagues<sup>5</sup> showed that IL-23 produced changes in the skin that mimicked the start of the psoriatic process. Adding IL-23 to skin organotypic cultures resulted in a pattern of cytokine expression, including cytokines in the IL-20 family, that resembled that seen in psoriasis. For the first time, the observations about the IL-20 subfamily made it possible to demonstrate a direct connection between the immune system and the skin. An avenue of research into novel treatments was now appreciated.

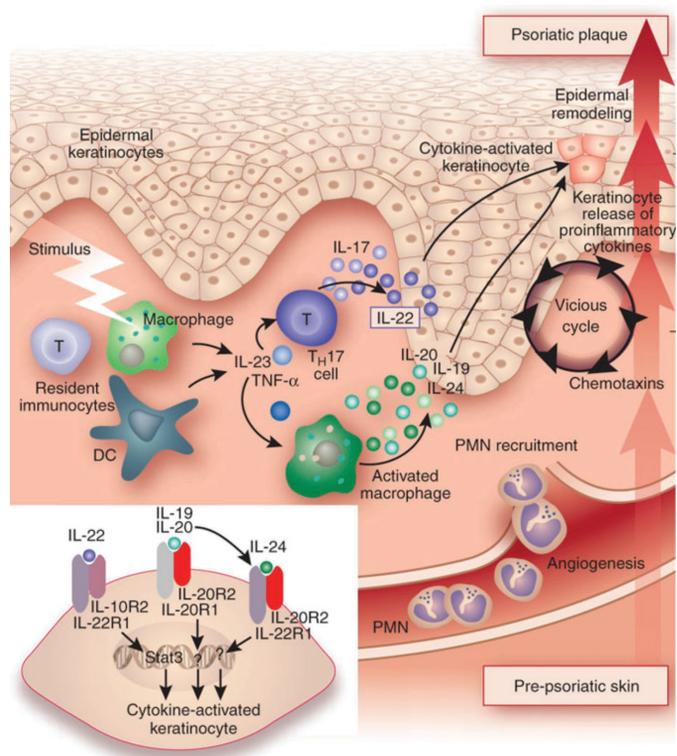
### Disease Pathways: Implications for Therapy

Much of the research and clinical focus in psoriasis in the next 5 years, at least, will be on different elements of these pathways and the ways that this knowledge can be exploited to develop new therapeutic interventions. The surge of studies within the past 5 to 6 years—and the resultant flood of information—has resulted in necessary and ongoing discussion, analysis, and synthesis of new data and concepts.

As new information has emerged on each newly recognized pathway in psoriasis—including the events that happen upstream and downstream of each, as well as the molecules involved—the natural tendency is to focus on specific pathways, events, and molecules. This focus on specifics is necessary for new pathophysiologic targets to be addressed—whether tumor necrosis factor (TNF), interleukins, or any other inflammatory protein and their respective pathways of activity.

However, it is also important to be able to refocus the lens of attention to appreciate that targeting one element of a specific pathway does not necessarily preclude the importance of other elements in the pathway(s). For example, IL-17, a cytokine that was initially thought to be only primarily responsible for the persistence of the immune reaction in psoriasis,<sup>6</sup> is the focus of a great deal of current research focus.

It has become clearer over time that targeting TNF and IL-23 actually downregulates cytokines in the IL-17 system, which includes a number of proteins such as IL-17A and IL-17F. Another protein in this family, IL-17C, is a feedback loop produced by keratinocytes.<sup>7</sup> A number of observations make IL-17A a rational target to consider for direct inhibition. The TNF inhibitors have a broad inhibitor action across both the innate and the adaptive immune responses,<sup>8,9</sup> and the IL-12/23 inhibitors block T-cell differentiation and broad inhibitor actions. Small-molecule kinase inhibitors or immunomodulators also have broad inhibitory actions across immune cells, as well as other cell types; these agents act intracellularly to inhibit cells.<sup>9</sup> Furthermore, IL-17R inhibitors act at the level of the cytokine receptor.<sup>9,10</sup> Immune inhibition by anti-IL-17A has the potential to affect only IL-17A signaling, preserving other functions of the immune system.<sup>8</sup>



**FIGURE 1** Complex Interactions of Cytokine Pathways in Psoriasis. DC=dendritic cell; IL=interleukin; PMN=polymorphonuclear leukocyte; TH=T helper; TNF=tumor necrosis factor. Source: Nickoloff BJ. Cracking the cytokine code in psoriasis. *Nat Med*. 2007;13:242-244. Used with permission.

Thus, as **Figure 1** illustrates, what is known about psoriasis pathophysiology to date creates a complex, interactive image<sup>9</sup>; ultimately, the entire picture must be in the frame. This view is important both for the therapeutic implications in controlling the signs and symptoms of psoriasis and for appreciating the potential effects—positive or negative—of various treatment options on the inflammatory comorbid conditions that are now recognized in psoriasis.

### Inflammatory Pathways and Comorbidities in Psoriasis

Accumulated data over the past 10 years demonstrate that the inherent health risks associated with psoriasis extend beyond skin lesions. Indeed, psoriasis is associated with many comorbid inflammatory diseases that affect many different organ systems. Thus, psoriasis must be recognized as a cutaneous marker of systemic inflammatory disease.

Psoriasis is associated with multiple disease states and behaviors that have the potential to increase morbidity and mortality and adversely affect quality of life. These include psoriatic arthritis, Crohn's disease, uveitis, depression, alcoholism, and cigarette smoking.

### Psoriasis and Cardiovascular Disease

Psoriasis is epidemiologically associated with multiple comorbidities that increase the risk for cardiovascular disease, including hypertension, diabetes mellitus, dyslipidemia, and obesity. Importantly, even in patients who do not have those cardiovascular risk factors, psoriasis is independently associated with an increased risk for myocardial infarction (MI).<sup>11</sup>

Psoriasis as an independent risk factor for MI was shown clearly in a prospective, population-based cohort study using data captured in the United Kingdom, in which the investigators compared outcomes among patients with and without a diagnosis of psoriasis in the General Practice Research Database.<sup>11</sup> Patients with mild psoriasis (n=127,139), those with severe psoriasis (n=3,837), and 556,995 controls were identified. Patients ranged in age from 20 to 90 years. Within the control population, 11,194 MIs (2.0%) were reported; 2,319 (1.8%) MIs occurred in the group of patients with mild psoriasis, and 112 (2.9%) occurred in the group with severe psoriasis. The incidence per 1,000 person years in the control group without psoriasis was 3.58 (95% CI, 3.52-3.65); the incidence in the group with mild psoriasis was 4.04 (95% CI, 3.88-4.21), and the incidence of MI in the group with severe psoriasis was 5.13 (95% CI, 4.22-6.17). Interestingly, the relative risk for MI varied according to patient age and disease severity, with the relative risk for MI being higher in patients with severe disease, particularly among the younger age groups. The investigators did not publish the adjusted relative risks (RRs) for each decade studied between 20 and 80 years of age, but they highlighted the data for 30- and 60-year-olds as examples. As shown in **Figure 2**, a 30-year-old patient with mild psoriasis had an adjusted RR for MI of 1.29 (95% CI, 1.14-1.46) vs 1.08 (95% CI, 1.03-1.13) for a 60-year-old with mild psoriasis. A 30-year-old patient with severe psoriasis had an adjusted RR for MI of 3.10 (95% CI, 1.98-4.86) vs 1.36 (1.13-1.64) for a 60-year-old with severe disease.

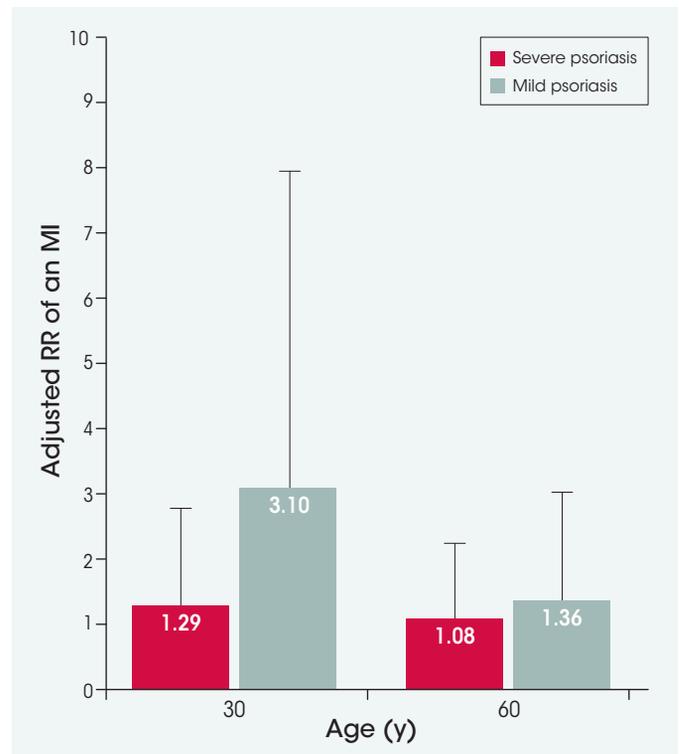
Epidemiologic studies have demonstrated that severe psoriasis is associated with an increased prevalence of the metabolic syndrome,<sup>12-14</sup> a chronic inflammatory state that is associated with cardiovascular mortality.<sup>15,16</sup>

These comorbid associations hold true for not only adult but also pediatric patients with psoriasis. In an international study of 18 dermatology centers on four continents, Paller and colleagues<sup>17</sup> found that among 600 pediatric patients with psoriasis when compared with healthy controls, the children with psoriasis, regardless of disease severity, were much more likely to be overweight or obese.

#### Mechanisms of Cardiovascular Risk in Psoriasis

Kremers and colleagues<sup>18</sup> proposed three possible main causes for cardiovascular risk in psoriasis that include (1) the use of dyslipidemic therapies such as corticosteroids, acitretin, and cyclosporine, (2) the increased prevalence of associated and/or independent risk factors (smoking, obesity, hypertension, and alcohol misuse), and (3) uncontrolled inflammation leading to endothelial dysfunction and dyslipidemia. However, a number of studies of MI risk in psoriasis that controlled for dyslipidemic therapies and risk factors such as cigarette smoking, obesity, hypertension, and alcohol use confirmed that psoriasis is an independent risk factor for MI.<sup>19,20</sup> Accumulating evidence suggests that psoriasis is associated with uncontrolled inflammation that subsequently leads to vascular endothelial dysfunction, atherosclerosis, and dyslipidemia, all contributing to atherosclerotic plaque formation.

Interestingly, Wu and colleagues<sup>21</sup> recently showed that TNF inhibitors might reduce MI risk in a large, retrospective cohort



■ **FIGURE 2** Risk of MI in Patients With Psoriasis.

MI=myocardial infarction; RR=relative risk.

Source: Adapted from Gelfand et al.<sup>11</sup>

study of patients with psoriasis treated in the Kaiser Permanente Southern California health plan. Records of 8,845 patients were included; 1,673 had received an anti-TNF biologic agent for at least 2 months, 2,097 had not been treated with a TNF inhibitor but had received other systemic agents or phototherapy, and 5,075 had used only topical agents and had not been treated with TNF inhibitors, other systemic treatments, or phototherapy. Follow-up ranged from 2.9 to 5.5 years (median duration, 4.3 years). The duration of treatment with TNF agents ranged from 215 to 1,312 days (median duration, 685 days).

The incidence of MI in the TNF inhibitor group was 3.05/1,000 patient years; in the oral therapy and phototherapy group, the MI incidence was 3.85/1,000 patient years, and in the topical therapy group, the MI incidence was 6.73/1,000 patient years. The investigators adjusted the data for MI risk factors and reported that the adjusted hazard ratio for MI in the TNF-inhibitor cohort was significantly lower (adjusted hazard ratio, 0.50; 95% CI, 0.32-0.79) than in the topical cohort. In addition, the data revealed that the patients on oral systemic therapy or phototherapy also had a significantly lower risk ratio than did the topical cohort (adjusted hazard ratio, 0.57; 95% CI, 0.41-0.81).

In the Kaiser Permanente study, the MI risk ratio was lower in the TNF cohort than in the oral systemic therapy/phototherapy cohort, but the difference was not statistically significant. Similar results were seen in the large epidemiologic study from the Danish population, discussed above.<sup>20</sup> These data suggest that effectively reducing systemic inflammation in psoriasis, regardless of the therapeutic modality employed, may reduce cardiovascular risk.

### Implications for Dermatologists

Given the comorbid conditions that can be associated with psoriasis, dermatologists should consider screening patients—particularly those with moderate to severe disease—to identify those in whom cardiovascular risk reduction may be appropriate. Proposed basic steps to screening are basic laboratory evaluations (including fasting metabolic panel and lipid levels), regular monitoring of blood pressure and weight, and inquiry about symptoms of arthritis, alcohol and tobacco use, and depression. In addition, it is possible that the potential for cardiovascular risk—especially MI risk—in patients with moderate to severe psoriasis may outweigh the risks for adverse events associated with systemic therapies used to treat the disease.

### Conclusion

The understanding of psoriasis pathophysiology has advanced substantially and, in the past 5 to 7 years, has changed rapidly. Deciphering the IL-17 pathway has established the connection between immunity and the skin that had been presumed to exist but had heretofore not been identified. The importance of this connection is evident in the current research for more targeted therapeutic agents. However, this does not preclude the importance of all the other elements in the pathophysiologic pathways that already are effectively targeted with existing agents.

The advances in understanding the pathophysiologic inflammatory pathways also have led to greater recognition of the importance of immune-mediated comorbid diseases, particularly cardiovascular disease. Patients with moderate to severe psoriasis are at greater risk than are those with mild disease, but mild psoriasis is a systemic inflammatory condition that possibly confers increased risk to the patient.

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