Research gaps in psoriasis: Opportunities for future studies

Caitriona Ryan, MD,a Neil J. Korman, MD, PhD,b Joel M. Gelfand, MD, MSCE,c,k Henry W. Lim, MD,d Craig A. Elmets, MD, Steven R. Feldman, MD, PhD, Alice B. Gottlieb, MD, PhD, John Y. M. Koo, MD, Mark Lebwohl, MD, Craig L. Leonardi, MD, Abby S. Van Voorhees, MD, Reva Bhushan, PhD, and Alan Menter, MD

Dallas, Texas; Cleveland, Ohio; Philadelphia, Pennsylvania; Detroit, Michigan; Birmingham, Alabama; Winston-Salem, North Carolina; Boston, Massachusetts; San Francisco, California; New York, New York; St Louis, Missouri; and Schaumburg, Illinois

Over the past 2 decades, considerable progress has been made to further elucidate the complex pathogenesis of psoriasis, facilitating the development of a new armamentarium of more effective, targeted therapies. Despite these important advances, substantial deficits remain in our understanding of psoriasis and its treatment, necessitating further research in many areas. In the sixth section of the American Academy of Dermatology Psoriasis Guidelines of Care, gaps in research and care were identified. We discuss the most important gaps in research that currently exist and make suggestions for studies that should be performed to address these deficits. These encompass both basic science and clinical research studies, including large, prospective epidemiologic studies to determine the true prevalence and natural history of psoriasis; further molecular studies in patients with psoriatic and psoriatic arthritis to understand the function of psoriasis susceptibility genes and to identify novel therapeutic targets; studies to examine the role of environmental factors in the development of psoriasis; further investigation of the relationship between psoriasis and cardiometabolic disease; studies that examine the role of adjunctive therapies such as psychological interventions in appropriate patient groups; and finally, studies to identify biomarkers of disease severity and treatment response to optimize patient therapy. (J Am Acad Dermatol 2014;70:146-67.)

Key words: adjunctive therapies; biologics; cardiovascular disease; comorbidities in psoriasis; comparative studies; disease severity; environmental factors in the development of psoriasis; future research studies; methotrexate; molecular studies in psoriatic and psoriatic arthritis; pathomechanisms and genetics of psoriasis; phototherapy; psoriasis; psoriasis guidelines; psoriasis treatment; psoriatic arthritis; psychological; research gaps; therapeutic targets; topical therapies.

Although tremendous progress has been made in recent years regarding our understanding of the pathogenesis and treatment of psoriasis, there are still significant gaps in our knowledge base. In this article, we will address some of the more prominent and important gaps in research that currently exist and make suggestions for studies that should be performed to address these gaps.

Significant advances have been made in unraveling the complex genetic basis of psoriasis and in identifying inflammatory pathways important in disease pathogenesis. This has facilitated the development of several new, more selective biologic
agents, many of which are in clinical development. Further understanding of the immunopathogenesis of psoriasis and psoriatic arthritis (PsA) may allow the identification of more efficacious, highly targeted therapies. In an era of rapidly advancing molecular technology, the functional relevance of all currently known psoriasis susceptibility genes needs to be fully elucidated, particularly for different disease phenotypes. Further research is needed to examine the natural history of psoriasis and factors that determine disease prognosis. The wide spectrum of comorbidities observed in patients with psoriasis is ever-growing. Patients with psoriasis have an increased prevalence of cardiovascular disease, diabetes, hypertension, hyperlipidemia, obesity, inflammatory bowel disease, obstructive sleep apnea, steato-hepatitis, and psychiatric disorders. The mechanistic pathways leading to these comorbid conditions need to be fully elucidated. Further research and interventions to adequately screen for and treat the psychological and cardiovascular comorbidities associated with psoriasis are also warranted.

METHODS

A work group of 12 recognized psoriasis experts was convened to produce the American Academy of Dermatology Psoriasis Guidelines of Care. The sixth and final section of these guidelines listed several current gaps in psoriasis research and care. This review further expands on these deficiencies in our knowledge base and makes suggestions for further studies to address these research gaps. A search of the MEDLINE database spanning from inception to March 2013 was performed to ensure adequate studies had not been done in each of the proposed research areas. Only English-language publications were reviewed. Once a review of current research gaps was formulated, each expert gave their critical appraisal of the evidence presented. All work group members completed a disclosure of commercial support.

Clinical features

The global incidence and prevalence of psoriasis has not been comprehensively studied (Table I). A recent systematic review of published population-based studies examined the prevalence and incidence of psoriasis worldwide. The prevalence varied from 0.91% in the United States to 8.5% in Norway, with higher frequencies observed in countries of higher latitude. Further research is needed to examine trends in incidence over time and the prevalence of psoriasis-associated comorbidities according to age and geographic region.

There have been no large, broadly representative, prospective, longitudinal studies specifically designed to evaluate the natural history of psoriasis. Our knowledge of the natural history of psoriasis is largely derived from large cross-sectional studies, the psoralen plus ultraviolet (UV) A cohort study, and analyses of data from administrative and medical record databases. The largest cross-sectional study of psoriasis in the United States, performed over 35 years ago, suggested that spontaneous remission may occur in up to one third of patients. Studies are needed to validate this frequency and characterize factors associated with spontaneous remission for different phenotypes of psoriasis, including disease severity, age, morphologic attributes of plaques, and patient comorbidities. Comprehensive profiling of patients who experience spontaneous remission of psoriasis may yield insight into factors that determine chronicity of the disease. Small studies have also shown that classifying patients with chronic plaque psoriasis into those with thin or thick plaques may have implications for the clinical course of disease.

The Centers for Disease Control and Prevention recently issued recommendations for a public health research agenda addressing the need for further public health research in psoriasis and PsA, which should increase awareness and understanding of psoriasis and its associated comorbidities from a public health perspective. Expert consultants identified and discussed key issues pertinent to the development of a public health agenda and reviewed the existing peer-reviewed, public health literature to inform knowledge gaps for each key issue (Table I).
Table I. Proposed studies to address research gaps in clinical features of psoriasis

<table>
<thead>
<tr>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Large, broadly representative, prospective, longitudinal studies designed to evaluate the natural history of psoriasis.</td>
</tr>
<tr>
<td>2. Large, prospective, longitudinal studies of psoriasis that obtained genetic information to evaluate clinical and genetic factors that influence clinical phenotype and severity of skin disease.</td>
</tr>
<tr>
<td>3. Studies that evaluate trends in incidence over time and the prevalence of psoriasis-associated comorbidities according to age and geographic region.</td>
</tr>
<tr>
<td>4. Studies to characterize the factors associated with spontaneous remission for different phenotypes of psoriasis, including genetics, disease severity, age, morphologic attributes of plaques.</td>
</tr>
</tbody>
</table>

Table II. Key public health agenda topics and relevant specifics identified by the Centers for Disease Control and Prevention for psoriasis and psoriatic arthritis research

<table>
<thead>
<tr>
<th>Topic</th>
<th>Specifics</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Case definitions</td>
<td>- Validation study to determine the best public health surveillance case definitions</td>
</tr>
<tr>
<td></td>
<td>- Examine potential to use existing psoriatic arthritis screening tools</td>
</tr>
<tr>
<td>2. Prevalence and disparities</td>
<td>- Update prevalence estimates with most recent data available</td>
</tr>
<tr>
<td></td>
<td>- Examine prevalence at all levels of severity</td>
</tr>
<tr>
<td></td>
<td>- Examine disparities (eg, age, gender, racial/ethnic)</td>
</tr>
<tr>
<td></td>
<td>- Define the prevalence and characteristics of those with undiagnosed psoriasis</td>
</tr>
<tr>
<td>3. Severity</td>
<td>- Examine disease severity in the pediatric population</td>
</tr>
<tr>
<td></td>
<td>- Examine disease severity in the adult population</td>
</tr>
<tr>
<td></td>
<td>- Determine the best measures of disease severity for population-based studies</td>
</tr>
<tr>
<td>4. Cost</td>
<td>- Update direct cost estimates with the most recent data</td>
</tr>
<tr>
<td></td>
<td>- Update indirect cost estimates with the most recent data</td>
</tr>
<tr>
<td></td>
<td>- Examine the relationship between cost and disease severity</td>
</tr>
<tr>
<td>5. Employment/ability to work</td>
<td>- Examine the impact on employment and/or ability to work</td>
</tr>
<tr>
<td></td>
<td>- Determine if the diseases impact income and health insurance coverage</td>
</tr>
<tr>
<td>6. Health care</td>
<td>- Examine health care use</td>
</tr>
</tbody>
</table>

our understanding of the pathogenesis of psoriasis. This has facilitated the identification of new therapeutic targets and the development of more selective biologic agents. Continued research is required, however, to fully elucidate the complex immunopathogenesis of this disease (Table III).

**Genetics.** The genetic complexity of psoriasis has become increasingly clear and recent genome-wide association studies have identified 32 psoriasis susceptibility regions. The Psoriasis Immunochip Consortium, a multicenter project developed to validate previously discovered loci and to identify new loci, has identified 15 new highly significant single nucleotide polymorphisms, including loci associated with regulation of T-cell function, interferon (IFN)-mediated antiviral responses, macrophage activation, and nuclear factor-κB signaling. Further research should identify these implicated genes and ascertain their functional role in the development of psoriasis. Many are associated with immune pathways, suggesting that genetic variation may be directly responsible for dysregulation of inflammatory pathways in psoriasis, whereas others are responsible for skin barrier function and epidermal proliferation. Further investigation is thus needed to explore whether the genetic basis of psoriasis stems from a primary defect in immunologic function, a defect in keratinocyte function, or a complex interaction of both. With the continued decreasing cost of gene sequencing, fine mapping of psoriasis susceptibility loci is becoming more feasible.

Studies evaluating the correlation between psoriasis genotype and phenotype are needed. There is considerable controversy as to whether psoriasis and PsA constitute genetically distinct diseases or share the same inheritance pattern. Genetic differences have recently been identified in patients with joint involvement and in patients with pustular psoriasis. Population-based studies show that the heritability of PsA is 3 to 5 times higher than that of psoriasis, and variants of several genes in the nuclear factor-κB signaling network and the T helper 17 cell/interleukin-23 (Th17/IL-23) pathway are
Immunology. Psoriasis research has recently been revolutionized by increased understanding of the pivotal role of the Th17/IL-23 axis in disease pathogenesis.\textsuperscript{27} Other inflammatory cell subsets including regulatory T cells, natural killer cells, dendritic cells, and macrophages, along with keratinocytes and endothelial cells may also be important in pathogenesis.\textsuperscript{28-31} More work is needed to define the roles of individual inflammatory cell subsets in the skin and blood of patients with psoriasis and to elucidate downstream pathways and inflammatory mediators in psoriasis pathogenesis. The ultimate goal in psoriasis immunologic research is to develop targeted therapies that correct immunologic dysregulation without suppressing protective immunity and increasing the risk of more global immunosuppression. The potential roles of toll-like receptor ligands, inflammatory cytokines, chemokines, adipokines, growth factors, adhesion molecules, angiogenic factors, and neuroptides in disease pathogenesis have also been suggested.\textsuperscript{27,32}

Changes in expression of small regulatory RNAs such as microRNAs provide further insights into the pathogenesis of psoriasis. There is significant differential expression of microRNAs in psoriatic skin, particularly in microRNAs involved in epithelial differentiation, immune quiescence, and angiogenesis.\textsuperscript{33} Other epigenetic alterations, such as CpG methylation status or histone modifications, may play a role in pathogenesis. There are significant CpG methylation differences among lesional skin, nonlesional psoriatic skin, and normal-appearing skin, which warrant further investigation.\textsuperscript{34}

Angiogenesis. The role of angiogenesis and the vascular bed in the pathogenesis of psoriasis has received little attention. Polymorphisms of vascular endothelial growth factor (VEGF) are associated with an increased susceptibility to psoriasis, up-regulation of angiogenesis occurs early in the development of psoriasis lesions, and overexpression of VEGF isoforms is also observed in nonlesional psoriatic skin compared with that of healthy donors.\textsuperscript{35-37} Therapeutic inhibition of angiogenesis may be of benefit in the treatment of psoriasis by blocking recruitment of leukocytes driving cutaneous inflammation. Both topical and systemic anti-VEGF antibody treatment in psoriasis mice models results in clinical improvement of psoriasiform disease.\textsuperscript{38} One patient with psoriasis and concurrent cancer who was treated with bevacizumab, an anti-VEGF therapy, completely cleared.\textsuperscript{39} Thus, targeting angiogenesis with topical or systemic antibodies could have a therapeautic benefit in psoriasis.

Table III. Proposed studies to address research gaps in genetics and pathophysiology of psoriasis

<table>
<thead>
<tr>
<th>Pathophysiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Studies evaluating the correlation between psoriasis genotype and clinical phenotype</td>
</tr>
<tr>
<td>2. International collaborative networks to provide increased power to explore the genetics of psoriasis</td>
</tr>
<tr>
<td>3. Elucidation of differences in molecular pathways for different psoriasis phenotypes, including guttate,</td>
</tr>
<tr>
<td>erythrodermic, inverse, palmoplantar, and generalized pustular psoriasis</td>
</tr>
<tr>
<td>4. Understanding specific molecular pathways unique to psoriatic arthritis to facilitate the development</td>
</tr>
<tr>
<td>of novel targeted therapies to treat joint involvement</td>
</tr>
<tr>
<td>5. Identification of psoriasis antigens that trigger the inflammatory cascade in genetically susceptible</td>
</tr>
<tr>
<td>patients</td>
</tr>
<tr>
<td>6. Investigation of possible alterations in the epidermal barrier in psoriatic skin that influence the</td>
</tr>
<tr>
<td>development or propagation of psoriasis</td>
</tr>
<tr>
<td>7. Better understanding of the role of angiogenesis and neurogenic inflammation in the development of</td>
</tr>
<tr>
<td>psoriasis to facilitate the development of novel targeted therapies</td>
</tr>
<tr>
<td>8. Studies to assess the influence of smoking, alcohol, and obesity on the natural course of the disease,</td>
</tr>
<tr>
<td>either by preventing its development or reducing its severity</td>
</tr>
</tbody>
</table>

observed in higher frequency in patients with PsA.\textsuperscript{14,21-23} Certain genes are also more frequently associated with specific phenotypes of PsA.\textsuperscript{24-26} Further investigation of the functional relevance of these genetic variations and close collaboration with our rheumatology colleagues will be required to identify more specific therapeutic targets for PsA.

Mutations in the interleukin (IL)-36RN gene, which encodes the IL-36 receptor antagonist, can lead to generalized pustular psoriasis.\textsuperscript{40} Little is known, however, about the genetics of other pustular variants, such as palmoplantar pustulosis or acrodermatitis continua of Hallopeau.

The establishment of international collaborative networks is critical to better understand the genetics of psoriasis. Future studies using next-generation sequencing technologies will allow interrogation of whole-genome sequence data. The International Psoriasis Council has a current genetic proposal entitled “Towards Completing the Genetic Map of Psoriasis: Rare Protein Altering Variants in 10,000 Psoriasis Cases and 10,000 Controls,” which aims to systematically evaluate the contribution of common and rare coding variants to disease susceptibility in 10,000 psoriasis cases and 10,000 controls using an exome chip.
**Neurogenic inflammation.** The potential role of neuropeptides and cutaneous neurogenic inflammation in psoriasis pathogenesis also warrants further study.\(^\text{40}\) Elevated psychological stress levels are recognized triggers for exacerbations of psoriasis, but the mechanisms underlying this phenomenon are not understood. Patients with psoriasis whose disease is stress responsive show an impaired response of the hypothalamus-pituitary-adrenal axis to psychological stress.\(^\text{41}\) Substance P has been suggested as a potential mediator accounting for the temporal onset of psoriasis with stress.\(^\text{32}\) Both the corticotropin-releasing hormone and adrenocorticotropic hormone receptors are expressed at higher levels in psoriatic skin compared with normal-appearing skin, and may also play a role in stress-mediated exacerbations of psoriasis.\(^\text{43-45}\) The immunologic effect of neuropeptides released by peripheral cutaneous nerves may allow higher neural centers to modulate immune response both at a systemic and a local level. Cutaneous sensory nerves may act as a link between the nervous and the immune response, and numerous reports of increased levels of nerve growth factor, vasoactive intestinal peptide, calcitonin gene-related peptide, and neurotensin in lesional and nonlesional psoriatic skin support this theory.\(^\text{32}\) Studies using the psoriasis mouse model based on transgenic overexpression of the angiopoietin receptor in keratinocytes took advantage of the observation that psoriatic plaques resolve in areas of denervated skin.\(^\text{40,46,47}\) In this model of nerve injury, sensory nerve-derived peptides were shown to mediate dendritic cell (DC) and T-cell infiltration into skin and that denervation reverses the psoriasis phenotype.\(^\text{48}\) The use of neuropeptide modulating agents may present a potential therapeutic option for psoriasis.

**Environmental factors.** Environmental risk factors, which predispose to the development of psoriasis or contribute to disease exacerbations, remain poorly defined.\(^\text{9,11}\) The initiation, maintenance, and subsequent exacerbation of psoriatic lesions is dependent on a complex interplay among genetic, environmental, and lifestyle risk factors such as infectious agents, stress, physical trauma, obesity, diet, alcohol, smoking, and medications in genetically predisposed individuals. With increasing knowledge of epigenetic phenomena and transcriptional influences, the mechanisms through which these environmental influences mediate their effects may now be further investigated. Although it is possible that modification of environmental influences and lifestyle choices such as smoking, alcohol, and obesity in patients with psoriasis may positively influence the severity of disease, there are no studies to validate the causality of these factors.\(^\text{49-52}\)

Smoking negatively impacts the course of psoriasis and can render patients less responsive to treatment.\(^\text{49,50}\) Smokers have higher circulating Th17 cell levels than nonsmokers, and tobacco smoke extract induces Th17 generation from central memory T cells and the expression of IL-17 and IL-22 in vitro.\(^\text{53}\) Further studies should examine how cigarette smoking activates the Th17 axis and whether other environmental influences are mediated by this pathway. Although the frequency of smoking and excess alcohol consumption is increased in patients with psoriasis, it remains to be determined whether these are specific risk factors, or if the associated psychological distress leads to this lifestyle choice.\(^\text{49,51,54}\)

The study of evolutionary genetics suggests that genetic variants conferring protection to particular endemic infections may increase susceptibility to autoimmune disease and that adaptive immunity toward pathogenic microbes may be an initiating signal for autoimmune diseases.\(^\text{55}\) Microbial agents including bacterial products, mycobacterium, and viral antigens have all been implicated in the pathogenesis of psoriasis. LL-37 cathelicidin, an antimicrobial protein, can form complexes with bacterial DNA, activating plasmacytoid dendritic cells to produce IFN-\(\alpha\) in early psoriasis lesions.\(^\text{56}\) Molecular mimicry may help to explain the prolonged immune dysregulation after a presumed initial microbial insult in psoriasis.\(^\text{57,58}\) There is significant evidence that \(\beta\)-hemolytic streptococcal infections can trigger and exacerbate psoriasis and it is postulated that the natural selection of psoriasis has been an evolutionary protective mechanism against overwhelming streptococcal infection.\(^\text{59}\) Current evidence, however, shows that antistreptococcal treatment does not significantly modify the course of cutaneous disease.\(^\text{60}\) Several studies have examined the microbiota of the skin of patients with psoriasis using parallel pyrosequencing of skin biopsy specimens and demonstrated significant differences in the composition and representation of the cutaneous bacterial microbiota, with an increase in *Streptococci*, and reductions in *Staphylococci* and *Propionibacteria* colonization in lesional psoriatic skin compared with that of healthy donors.\(^\text{51-63}\) It remains to be determined if these changes are of primary pathological significance or secondary alterations in previously diseased skin.

Alternatively, viral antigens may be the inciting stimulus for the development of psoriasis, leading to overproduction of IFN-\(\alpha\) and activation of
Plasmacytoid dendritic cells through toll-like receptors. Infection with Coxsackie adenovirus has been implicated in the cause of psoriasis, and HIV has been shown to trigger and or exacerbate psoriasis. Patients with psoriasis are enriched for genetic variants that limit the ability of HIV to replicate after infection resulting in a delayed progression to AIDS. Further investigation is needed to confirm whether initial infection by bacterial and viral microbes, or evolutionary mechanisms that increase host defense or immunity to particular infections, contribute to the development of psoriasis.

The mechanisms by which several very characteristic clinical phenomena in patients with psoriasis occur remain poorly understood. For example, there is little research to explain the Koebner phenomenon, which is observed in psoriasis and other inflammatory skin diseases. This is likely a result of the trauma-induced release of proinflammatory mediators, such as tumor necrosis factor (TNF)-alpha, IL-6, IFN-α, or IFN-γ, which then trigger or propagate the inflammatory cascade in nonlesional skin. In a xenotransplant model of psoriasis, psoriatic lesions develop spontaneously after engraftment of pretreatment human skin onto immunodeficient mice lacking T, B, and functional natural killer cells, suggesting that trauma induces changes in the local inflammatory cell milieu. This mechanism has yet to be comprehensively studied at a molecular, cellular, or protein level in vivo. Similarly, we have little understanding why psoriatic plaques have a predilection for particular body sites, such as the elbows, knees, and scalp and are distributed in a symmetric fashion. This may be mediated through similar mechanisms as the Koebner phenomenon in sites subject to trauma or may reflect the anatomic distribution of particular cutaneous nerves.

**Subpopulations**

Little is known about disparities in treatment and health-related quality of life in subpopulations of patients with psoriasis. The natural history and prognosis of disease, associated comorbidities, psychosocial issues, and treatment implications in subpopulations such as children, pregnant and lactating women, the elderly, and ethnic minorities requires more study (Table IV).

**Pediatric psoriasis.** Although children with psoriasis are very likely to be significantly affected by the psychological and stigmatizing effects of psoriasis, there is a relative dearth of clinical and scientific research in this patient population. Basic epidemiologic information on the demographics of pediatric psoriasis, including the role of family history, birthweight, and environmental influences on the course of psoriasis and its disease comorbidities is required. An international, pediatric database shows that children with psoriasis have excess adiposity and increased central adiposity regardless of psoriasis severity. This emphasizes the need for long-term, prospective programs to incorporate early monitoring and lifestyle modification into the treatment of children with psoriasis. There is also a higher incidence of psychiatric conditions in pediatric psoriasis. Research is needed to examine the psychological effects of psoriasis on children and the stigmatization they experience in social settings, particularly in school. Studies are needed to examine whether the incorporation of health education programs relating to chronic, disfiguring diseases in school curricula may impact on attitudes and the stigmatization of schoolchildren with psoriasis.

There is an urgent need for research studies to examine the use of systemic and biologic agents in pediatric patients with severe psoriasis, a group at high risk of devastating psychosocial effects. There has only been 1 randomized controlled clinical trial (RCT) to evaluate a biologic agent in children with psoriasis. This study showed that 57% of children treated with once-weekly etanercept achieved a 75% reduction in Psoriasis Area and Severity Index compared with 11% of placebo-treated children. Etanercept was well tolerated and there were no safety concerns, even with extended use. Unfortunately, although this study yielded promising results, further research is needed to better understand the safety and efficacy of biologic agents in pediatric patients with severe psoriasis.

**Table IV. Proposed studies to address research gaps in understanding the subpopulations of psoriasis**

<table>
<thead>
<tr>
<th>Subpopulations</th>
<th>Proposed Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Studies to collect basic epidemiologic information on pediatric psoriasis</td>
<td>1. Studies to collect basic epidemiologic information on pediatric psoriasis including the role of family history, birthweight, and environmental influences on the course of psoriasis and its comorbidities</td>
</tr>
<tr>
<td>2. Studies to evaluate the psychological effects of psoriasis in children</td>
<td>2. Studies to evaluate the psychological effects of psoriasis in children along with the stigmatization that they experience in the school setting</td>
</tr>
<tr>
<td>3. Studies to evaluate the use of both traditional systemic and biologic agents</td>
<td>3. Studies to evaluate the use of both traditional systemic and biologic agents in the treatment of moderate to severe pediatric psoriasis</td>
</tr>
<tr>
<td>4. Studies to evaluate the effect of psoriasis on pregnancy outcomes</td>
<td>4. Studies to evaluate the effect of psoriasis on pregnancy outcomes</td>
</tr>
<tr>
<td>5. Establishment of comprehensive pregnancy registries</td>
<td>5. Establishment of comprehensive pregnancy registries to evaluate the safety of topical, systemic, and biologic agents for psoriasis in pregnancy</td>
</tr>
<tr>
<td>6. Studies to evaluate the safety of breast-feeding in women treated with</td>
<td>6. Studies to evaluate the safety of breast-feeding in women treated with systemic or biologic agents</td>
</tr>
<tr>
<td>systemic or biologic agents</td>
<td></td>
</tr>
<tr>
<td>7. Studies to determine optimal treatment regimens and monitoring guidelines</td>
<td>7. Studies to determine optimal treatment regimens and monitoring guidelines for elderly patients with moderate to severe psoriasis</td>
</tr>
<tr>
<td>for elderly patients with moderate to severe psoriasis</td>
<td></td>
</tr>
</tbody>
</table>
results, etanercept was not approved for the pediatric population by the US Food and Drug Administration (FDA) although the European Medicine Agency approved its use in Europe. The reluctance of drug regulatory agencies to approve the use of immunosuppressant drugs in the pediatric population has had a detrimental impact on the management of pediatric psoriasis. This is a pressing issue, as it means that many US-based dermatologists prescribe these drugs off-label without the necessary labeling information to dose appropriately, or refuse to prescribe systemic agents for children who require aggressive therapy.74 The Best Pharmaceuticals for Children Act directed the National Institutes of Health (NIH) to sponsor pediatric clinical trials of drugs lacking patent protection if the FDA request for studies has been declined, but this has not been used for any psoriasis intervention to date.75 Resistance by drug regulatory agencies further deters pharmaceutical companies from performing clinical trials in children, an area already fraught with difficulty because of the complexities involved in obtaining institutional review board approval for pediatric studies in research centers. Reform of the drug approval process, allowing large, well-designed studies in the pediatric population, are urgently needed, especially with growing evidence that both metabolic and psychosocial comorbidities are more prevalent in younger patients with psoriasis.76,77

Pregnancy. Because the peak incidence of psoriasis occurs in the third decade of life, the effects of pregnancy on psoriasis and the safety and efficacy of various therapeutic agents in the treatment of pregnant women with psoriasis requires further study. This is particularly important as almost half of pregnancies in the United States are unplanned.76 Gaining a better understanding of why psoriasis improves or remains stable in the majority of patients during pregnancy but worsens in the postpartum period may provide valuable insights into how the hormonal milieu and immune-privileged state of pregnancy can modulate immune pathways.78

Little is known about the effect of psoriasis on pregnancy outcomes.78-80 Patients with psoriasis frequently have other comorbid medical conditions including diabetes and hypertension that may complicate pregnancy and increase the risk for complications. One case-control series comparing the pregnancy outcomes of 145 pregnant psoriatic women with 860 nonpsoriatic women suggested an increased risk of pregnancy complications with an increased incidence of recurrent abortions and chronic hypertension in patients with psoriasis.78 Further studies are needed to evaluate the impact of psoriasis on pregnancy outcomes.

Three reviews discuss issues relating to the management of psoriasis in pregnancy.78,80,81 Epidemiologic studies of pregnancy outcomes evaluating the use of topical, systemic, and biologic agents for psoriasis are essential. As controlled intervention studies cannot ethically be performed, large, comprehensive pregnancy registries are needed to evaluate the safety of these agents in pregnancy. Numerous pregnancy registries, including the Organization of Teratology Information Services registry and the cyclosporine registries have included pregnant patients with psoriasis undergoing systemic therapy.

There has been some controversy over the use of topical corticosteroids in pregnant women.82-84 One case-control study had suggested the use of topical corticosteroids in the first trimester of pregnancy increased the risk of oro-facial clefts.85 Another large population-based cohort study found a significant association between fetal growth restriction and maternal exposure to potent or highly potent topical corticosteroids but no increase in the risk of oro-facial cleft, preterm delivery, or fetal death.84 This area needs further study.

Cyclosporine passively crosses the placental blood barrier to achieve 10% to 50% of the maternal plasma concentration.86 The cyclosporine registries are the largest registries of any systemic psoriasis treatment to date, where the majority of our safety data comes from analyses of pregnancy outcomes in transplant recipients. Studies and meta-analyses of pregnancy outcomes from these registries have concluded that there is no evidence of teratogenicity and cyclosporine has been labeled as a category C drug by the FDA.87,88 Publication of the most recent cumulative results of cyclosporine pregnancy registries is needed. Other common traditional systemic agents such as acitretin and methotrexate cannot be used in pregnancy.79

Comprehensive, systematically collected information on the safety of the newer biologic therapies in pregnancy is lacking. Over the past decade, TNF-alfa inhibitors have been used in millions of patients for several inflammatory conditions, including a large number of women of childbearing age and are classified as pregnancy category B. Several small-scale retrospective studies support the relative safety of these agents in pregnant women, although there are reports of an increase in the rate of spontaneous abortions.79,89-91 This may be partly attributable to the underlying diseases. A review of over 120,000 adverse events in the FDA database revealed 61 congenital anomalies in 41 children born to mothers taking TNF-alfa inhibitors and postulated a potential association with the rare VACTERL syndrome, but this was
confirmed in only 1 child. There is 1 report of a fatal, disseminated bacillus Calmette-Guérin infection in an infant born to a woman who had remained on infliximab for Crohn’s disease during her pregnancy. Infliximab and adalimumab cross the placenta in the third trimester of pregnancy and there can be detectable levels in the serum of infants up to 6 months of age. As a result, registries are essential to monitor the long-term health of exposed infants and research is needed to define optimal vaccination schedules for infants exposed in utero. Ustekinumab is also designated as pregnancy category B. The product prescribing information states that ustekinumab should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. As of December 2010, 31 pregnancies have been reported with no reports of birth defects or fetal deaths. 

The treatment of psoriasis during pregnancy should take into consideration the benefit of the therapy to patient and fetus along with the availability of safer and effective alternatives. Current recommendations suggest the use of topical corticosteroids only if possible, with the use of narrowband (NB)-UVB phototherapy, TNF-alfa inhibitors, and cyclosporine reserved for more severe cases. 

Up to two thirds of women experience a worsening of their psoriasis in the postpartum period, which can require systemic treatment. As the majority of systemic drugs may be excreted in breast-milk, mothers are instructed not to nurse if systemic treatment is required. To date, evidence on the safety of breast-feeding during cyclosporine therapy is limited to 2 case series and 2 case reports. No adverse events related to maternal cyclosporine treatment during lactation have been observed, and cyclosporine concentrations in the blood of the infants were undetectable in all but 1 infant. Several case reports suggest the normal growth and development of children breast-fed during maternal treatment with TNF inhibitors, but comprehensive evidence and registry data are lacking. Case reports reveal negligible amounts of infliximab and etanercept in the breast-milk of lactating mothers. Ustekinumab is excreted in the milk of lactating monkeys administered ustekinumab. It is not known if ustekinumab is absorbed systemically through the immature neonatal gastrointestinal tract after ingestion. Further safety data are urgently needed to instruct guidelines on the management of psoriasis in pregnant and lactating women. 

The elderly. With an ever-aging population, more attention should be given to the treatment of psoriasis in the elderly, particularly with regard to monitoring for side effects of medications. Elderly patients typically have a higher prevalence of comorbid medical conditions, a greater number of concomitant medications, diminished renal function, and age-related changes in pharmacokinetics and pharmacodynamics of systemic medications. Currently, National Psoriasis Foundation guidelines are available for the treatment of psoriasis in the elderly but further research was recommended by the expert panel to optimize the treatment and monitoring of elderly patients with severe psoriasis.

Psoriatic arthritis
PsA is a debilitating inflammatory arthropathy, affecting approximately one quarter of patients with psoriasis. Considerable progress has been made in elucidating the immunologic and genetic basis of PsA, and in defining its epidemiologic and clinical features. Studies are needed to better understand the natural history of PsA in the dermatology setting, in particular to determine the true incidence, rate, and degree of joint destruction. More importantly, it is not yet understood why a particular subset of patient with psoriasis develop PsA. Understanding the genetic and immunologic differences between these psoriasis phenotypes may allow the development of novel targeted therapies that specifically treat joint involvement or, more importantly, prevent its development (Table V).

Growing evidence supports the idea that early diagnosis and treatment of PsA will reduce irreversible joint damage. The Swedish Early Psoriatic Arthritis Registry found that the early diagnosis of PsA was associated with lower joint disease activity at 5 years of follow-up. Moreover, early intervention with immune-modulating therapies may alter the clinical course of joint involvement. Patients with PsA who started taking etanercept within 2 years of disease onset had a superior improvement in pain assessments than those who commenced taking etanercept treatment after this time. This raises the question whether early initiation of systemic therapies may prevent or delay the onset of PsA in psoriatic patients who do not yet have joint involvement. Large, long-term, prospective cohort studies are needed to answer this question.

Currently, good screening tests and biomarkers to diagnose early PsA are limited. Early detection of PsA is difficult in the absence of a validated screening test but up to a third of patients in dermatology centers have undiagnosed PsA. Small studies have used magnetic resonance imaging for the early detection of PsA but much larger studies are needed. More research and close collaboration with our rheumatology colleagues will optimize...
Cardiometabolic comorbidities in psoriasis

There is a large and growing body of evidence that patients with moderate to severe psoriasis have a clinically significant increased risk of cardiovascular disease and cardiovascular risk factors such as diabetes mellitus, obesity, smoking, and the metabolic syndrome compared with the general population. Whether these comorbidities occur as a result of common susceptibility genes or as a result of systemic inflammation remains to be determined (Table V). Quite alarmingly, studies indicate that patients with severe psoriasis have excess mortality. The causes of death and the degree to which these are altered by psoriasis itself, its treatments, or comorbid behaviors also require further study (Table V).

There are 2 studies, however, that do not show an increase in cardiovascular risk, including the psoralen plus UVA cohort study, which collected prospective data over 3 decades. The psoralen plus UVA cohort study concluded that only patients with exceptionally severe psoriasis had an increased risk of overall mortality and that there was no significant risk of cardiovascular mortality. No association was observed between severe psoriasis and obesity or between obesity and cardiovascular mortality. As a result, this study has been the subject of considerable controversy, and it has been suggested that flaws in epidemiologic study design may account for its findings. Further adequately powered, long-term, prospective epidemiologic studies are needed to define the risk of cardiovascular disease in patients with psoriasis and the influence of objectively measured skin severity on this risk. Studies of patients with newly diagnosed incident psoriasis may be superior to those with long-term psoriasis at examining the inherent increase in cardiovascular risk, as inception cohorts minimize issues related to survivorship bias and would overcome the potential biasing effect of chronic inflammation contributing to observed risk.

Although it is well known that psoriasis is associated with a higher prevalence of obesity, there is debate as to whether obesity precedes, or follows, the development of psoriasis. Prospective studies show a graded association between body mass index and incident psoriasis, and patients with psoriasis have lipid abnormalities in the early stages of skin disease. Other studies suggest that obesity follows the development of psoriasis, implying that psoriatic inflammation or associated behaviors may contribute to the obese state. The degree to which obesity explains the higher risk of diabetes and metabolic syndrome observed in patients with psoriasis requires additional study, as several studies show that the increased risk of diabetes remains after accounting for obesity.
There are many hypothesized mechanisms to explain the complex relationship between psoriasis and cardiometabolic disease, but definitive evidence supporting any of these proposed pathways is lacking. It has been suggested that there may be co-inheritance of genes associated with psoriasis and genes associated with obesity, diabetes, and premature atherosclerosis but there is little evidence of shared susceptibility genes when comparing genome-wide association studies for psoriasis with those for obesity, diabetes, or premature atherosclerosis. It is more likely that the presence of systemic inflammation in patients with psoriasis may affect the function of other cells and tissues, leading to metabolic dysregulation, insulin resistance, and an increase in cardiovascular inflammation, often described as the “march of psoriasis.” Common inflammatory pathways are involved in the pathophysiology of psoriasis and cardiovascular inflammation, both of which are associated with a chronic proinflammatory, proangiogenic, and prothrombotic state, with similar inflammatory cell infiltrates and proinflammatory cytokine profiles. It has also been suggested that inflammation of adipose tissue leads to the release of proinflammatory adipokines that attenuate signaling through insulin receptors to produce a state of hyperinsulinemia. Increased understanding of the common molecular pathways underlying psoriasis, cardiovascular inflammation, and metabolic dysfunction may provide innovative approaches to treat psoriasis that might also decrease cardiovascular morbidity.

**Management of cardiometabolic risk.** Until alternative evidence is available, the presence of severe psoriasis should be considered an independent cardiovascular risk factor. As physicians, it is our responsibility to counsel patients with psoriasis regarding the increased risk of cardiometabolic conditions and the need for lifestyle modifications, including smoking cessation, weight reduction, and regular screening for diabetes and hypertension. Studies are required to ensure that patients have awareness of these associated conditions and are making lifestyle modifications accordingly. Further research to determine how to optimize primary prevention of cardiovascular events in patients with psoriasis is also required. It is of vital importance that standardized screening tools are developed to identify cardiometabolic comorbidities in routine clinical practice.

A more far-reaching advance in the research of comorbidities would be understanding if, and how, systemic treatment of psoriasis mitigates cardiometabolic risk. There is growing evidence to support the beneficial effect of systemic treatment on cardiovascular risk in the psoriatic and rheumatoid arthritis (RA) populations. In a retrospective cohort study of psoriasis and patients with RA, methotrexate reduced the risk of vascular disease compared with those who were not treated with methotrexate. Another study showed an increase in the protective cytokine adiponectin and a reduction in circulating C-reactive protein (CRP) after treatment of psoriasis with fumaric acid esters.

A large retrospective cohort study examined the effect of systemic treatment on the incidence of myocardial infarction (MI) in patients with psoriasis. After adjusting for cardiovascular risk factors, patients treated with TNF-alfa inhibitors had a significantly lower risk of MI compared with those treated with topical therapies alone, but there was no significant difference when TNF-alfa inhibitor use was compared with traditional systemic agents or phototherapy. A study evaluating the effect of etanercept on inflammatory biomarkers in psoriasis showed a significant decrease in CRP in patients with psoriasis and PsA. Another large-scale, retrospective cohort study of patients with RA or psoriasis showed that the adjusted risk of diabetes was lower for individuals starting to take TNF-alfa inhibitors or hydroxychloroquine compared with other nonbiologic disease-modifying agents such as methotrexate, suggesting that these agents may reduce the risk of metabolic dysfunction.

There has been considerable controversy regarding the association between the use of anti-IL-12p40 agents in patients with psoriasis and major adverse cardiovascular events (MACE). Despite 2 meta-analyses examining the use of anti-IL-12p40 inhibitors in psoriasis, conclusive evidence is not yet available regarding the effect of ustekinumab on cardiovascular risk. The first compared the excess probability of MACE in 22 RCTs in those receiving active treatment of anti-IL-12p40 agents (ustekinumab and briakinumab) and TNF-alfa inhibitors. Although the apparent increase in MACE observed with patients receiving anti-IL-12p40 antibodies was not statistically significant, the findings did raise questions about the cardiovascular safety of the anti-IL-12p40 agents, particularly as the short 12- to 24-week placebo-controlled period and small patient numbers may not have had adequate power to detect a real difference. A subsequent meta-analysis examining the rate of MACE in patients in RCTs of IL-12/23 antibodies showed a significantly higher risk of MACE in patients treated with anti-IL-12/23 agents compared with placebo. The discrepancy between these meta-analyses results from the use of different statistical methods to compare MACE rates. A 5-year safety study
conducted by the manufacturers of ustekinumab has shown no increase in the rate of MACE over time.\textsuperscript{140} With multiple new biologic treatments targeting the Th17/IL-23 axis currently in development, clinical studies to evaluate their effect on cardiovascular risk and molecular studies to further investigate the effect of these agents on vascular inflammation are essential.

Large multicenter, prospective RCTs are urgently needed to determine whether systemic or biologic therapies for psoriasis have a modulatory effect on cardiovascular comorbidities. As cardiovascular events are rare, surrogate outcome measures such as positron emission tomography-computed tomography scans of the coronary vasculature to measure dynamic vascular inflammation will be necessary to guide RCTs.

The impact of weight reduction on the clinical course of psoriasis and treatment response also needs further investigation. Anecdotal reports suggest that weight reduction may improve psoriasis and small case series have shown a beneficial effect of gastric bypass surgery on psoriasis.\textsuperscript{141,142} A study of cyclosporine in obese psoriatic patients showed a superior response when cyclosporine was combined with a calorie-controlled diet compared with cyclosporine alone.\textsuperscript{143} Further similar, well-designed, prospective studies of other systemic treatments in obese psoriatic patients are needed to examine if weight loss may supplement the response to pharmacologic therapies.

**Psychological comorbidities**

Psoriasis is associated with high rates of anxiety and depression and increased suicidal ideation, and causes a reduction in health-related quality of life comparable with other chronic diseases such as cancer and diabetes.\textsuperscript{144-146} Patients with psoriasis also have high levels of alexithymia, an inability to recognize or discuss feelings or emotional states. Depression in psoriasis may be partially attributed to the presence of a tonically overactive inflammatory response, as treatment with anti-TNF agents leads to an improvement in depressive symptoms.\textsuperscript{149}

Several mechanisms such as relaxation techniques and mindfulness meditation-based stress reduction interventions have reduced the distress associated with psoriasis but have shown limited efficacy in managing symptoms.\textsuperscript{150} Cognitive-behavioral therapy, however, has shown efficacy when combined with phototherapy compared with phototherapy alone.\textsuperscript{151} Further research is required into interventions that may lessen the psychosocial impact of psoriasis on disease-related quality of life. Dermatologists and psychologists should cooperate to optimize the treatment of psoriasis and its associated psychosocial burden to this end (Table V).

Psoriasis has a significant impact on sexuality and sexual relationships. Although sexual function is an integral component of quality of life, dermatology-specific and psoriasis-specific scales largely neglect the impact of disease on sexual function. When examining the stigmatization experience in psoriasis, involvement of the genitalia is most relevant, regardless of psoriasis severity.\textsuperscript{152} Although genital involvement can have devastating psychosexual implications for patients with psoriasis, few studies have examined its impact on quality of life and sexual functioning.\textsuperscript{155} Risk factors for the development of genital psoriasis, including gender, circumcision, obesity, smoking, the age of onset, and phenotypical associations such as scalp, nail, or joint involvement should be evaluated (Table V).

**Treatment**

Over the past decade, the delineation of new cellular and molecular pathways important in disease pathogenesis has facilitated the development of more selective agents, many of which are in clinical development. More research is needed to accurately assess the comparative efficacy and safety of both established and novel topical and systemic therapies (Table VI). The effectiveness of psoriasis therapies under real-world circumstances also requires further investigation as recent data suggest that psoriasis therapies have limited persistence and lower effectiveness in real-world settings compared with estimates derived from clinical trials.\textsuperscript{154}

**Topical therapies.** Topical therapies are the mainstay of therapy for most patients with psoriasis. Tachyphylaxis, a decreasing response to a physiologically active agent after multiple doses, is commonly described after the use of topical corticosteroids. Although tachyphylaxis can be demonstrated at a molecular level, only 1 small study has examined this phenomenon in the clinical setting and it showed no tachyphylaxis after the application of topical corticosteroid to psoriasis plaques twice daily for 12 weeks.\textsuperscript{156} Longer clinical and molecular studies are required to measure clinical response and receptor down-regulation over time with the use of topical corticosteroids, vitamin D analogs, and calcineurin inhibitors. The frequency of rebound flare after abrupt discontinuation of potent topical corticosteroids should also be examined. Studies evaluating the comparative effectiveness of topical agents in the scalp and intertriginous areas would be very helpful in further developing an evidence-based approach to topical therapy.
Table VI. Proposed studies to address research gaps in the treatment of psoriasis

<table>
<thead>
<tr>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Clinical and molecular studies to examine the frequency of tachyphylaxis with the monitored use of topical corticosteroids, vitamin-D analogs, and calcineurin inhibitors</td>
</tr>
<tr>
<td>2. Studies to evaluate the frequency of rebound flare after abrupt discontinuation of potent and superpotent topical corticosteroids</td>
</tr>
<tr>
<td>3. Studies on comparative effectiveness and adherence to topical agents in specific locations, eg, the scalp and intertriginous areas</td>
</tr>
<tr>
<td>4. Longer term studies on photocarcinogenic risk of NB-UVB therapy</td>
</tr>
<tr>
<td>5. Studies to examine the efficacy of combination of systemic and biologic treatments with NB-UVB</td>
</tr>
<tr>
<td>6. Large studies to evaluate the efficacy and safety profile of methotrexate</td>
</tr>
<tr>
<td>7. Studies to compare the efficacy of oral and parenteral administration of methotrexate</td>
</tr>
<tr>
<td>8. Studies to determine the optimum dosage and frequency of folic acid supplementation in methotrexate-treated patients</td>
</tr>
<tr>
<td>9. Further evaluation on the effectiveness of methotrexate for the treatment of psoriatic arthritis</td>
</tr>
<tr>
<td>10. Large, long-term, well-designed, comparator studies of systemic agents, which incorporate a placebo arm for at least 12 wk</td>
</tr>
<tr>
<td>11. Comparative effectiveness studies of psoriasis treatments for guttate, pustular, erythrodermic, inverse, and palmoplantar psoriasis</td>
</tr>
<tr>
<td>12. Studies combining biologics with traditional systemic agents in different dosage schedules compared with biologic agent monotherapy or systemic agent monotherapy</td>
</tr>
<tr>
<td>13. Long-term safety studies of 3 to 5 y for all new therapies to allow the detection of rare side effects or potentially beneficial effects, eg, a reduction in cardiovascular morbidity or prevention of the development of psoriatic arthritis</td>
</tr>
</tbody>
</table>

NB, Narrowband; UV, ultraviolet.

**Phototherapy.** UVB phototherapy is an effective and economical therapy that lacks many of the toxicities and immunosuppressive properties of traditional and biologic systemic therapies. Recent results from an ongoing study aimed to define the carcinogenic risk of NB-UVB show no significant association with skin cancer but the median cumulative number of treatments was only 29, with a median follow-up time of 5.5 years.\(^{156}\) Longer prospective studies are essential. Studies that examine the combination of systemic retinoids, methotrexate, or biologics with NB-UVB compared to monotherapy or NB-UVB alone are also needed.

Newer targeted therapeutic devices including laser and light-emitting diode devices are now available, or in late stages of development; they may have important implications for phototherapy.

**Methotrexate.** Methotrexate has been the first-line systemic agent for psoriasis for over 40 years but there are still many gaps in our knowledge regarding methotrexate.\(^{157}\) The use of methotrexate as a treatment for psoriasis is limited by unpredictable response and toxicity but only 2 small studies have evaluated the efficacy and safety of methotrexate in psoriasis.\(^{158,159}\) Although methotrexate was approved for psoriasis in 1971, most of the safety data for methotrexate have been extrapolated from RA studies. There is a higher frequency of nonalcoholic steatohepatitis and alcohol misuse in patients with psoriasis than in the RA population and patients with psoriasis have a higher risk of liver toxicity from methotrexate.\(^{2,54,160,162}\) Larger, well-designed studies are needed to determine the safety profile of methotrexate and to validate the current liver biopsy monitoring guidelines in the population of obese patients with psoriasis.\(^{160,161}\)

The bioavailability of methotrexate is higher with parenteral administration and the incidence of gastrointestinal side effects may be reduced in patients treated in this fashion. Moreover, injectable methotrexate is considerably less expensive in many countries. Comparative efficacy studies of oral versus parenteral administration of methotrexate in psoriasis would yield important information that would help to guide methotrexate-dosing recommendations. There is wide variation in the dose of folic acid supplementation used internationally and within the United States. Physicians prescribe dosages of between 800 \(\mu g\) and 5 mg daily, and practices vary greatly with regards to supplementation on the day of methotrexate administration—some physicians advocate doubling the dose to minimize side effects, whereas others omit folic acid because of concerns that it may decrease efficacy if administered with methotrexate. Well-designed studies to determine the optimum dosage and frequency of folic acid supplementation are needed.

Methotrexate has been considered a first-line treatment for PsA for many years. A recent RCT of 221 patients with PsA treated with methotrexate or placebo, however, showed no significant effect on PsA response as measured by several criteria.\(^{163}\) The only appreciable benefits of methotrexate treatment were reductions in both patient and assessor global scores and in skin scores at 6 months, raising questions about the role of methotrexate in PsA therapy, which would entail fundamental changes in
treatment algorithms for PsA. There has been considerable controversy among dermatologists and rheumatologists regarding this study, particularly regarding the low target dose of methotrexate used and the severity of arthritis in the patients enrolled. An open-label study examining infliximab given with methotrexate compared with methotrexate alone showed superiority of the combination treatment at 16 weeks but those in the methotrexate monotherapy group also had a favorable response, with 66.7% of patients achieving a favorable response with 66.7% of patients achieving an American College of Rheumatology (ACR)-20 response. Further randomized, placebo-controlled studies are urgently needed to confirm or refute the value of methotrexate in the treatment of PsA.

Aminopterin (4-amino-pteroyl-glutamic acid) is an antifolate drug that is structurally very similar to methotrexate. It was used between 1953 and 1964 for the treatment of psoriasis and pediatric acute leukemia before the advent of methotrexate, but production of aminopterin was discontinued for what appeared to have been manufacturing preferences for methotrexate. Animal and human clinical studies comparing aminopterin and methotrexate show that aminopterin has improved mean oral bioavailability, accumulates less in the cerebrospinal fluid, has less of an effect on erythropoiesis, and causes less increases in serum liver transaminases. As a result, aminopterin is now being studied for use in psoriasis and other inflammatory conditions.

Comparative studies. The comparative efficacy of psoriasis treatments for chronic plaque psoriasis is understudied and the few existing comparative studies are short term. There is a recent initiative from the NIH and the Patient-Centered Outcomes Research Institute to fund comparative effectiveness research, which will hopefully lead to more comparative efficacy studies in psoriasis. The first study to compare the efficacy of 2 biologic agents in psoriasis was a single-blind randomized study comparing the safety and efficacy of ustekinumab with etanercept. This study lacked a placebo arm, however, and the direct comparator phase lasted only 12 weeks. Large, long-term, well-designed, direct comparator studies of systemic agents, incorporating a placebo arm for at least 12 weeks, are necessary. Furthermore, the comparative efficacy of psoriasis treatments for clinical variants including guttate psoriasis, pustular psoriasis, erythrodermic psoriasis, inverse psoriasis, and palmoplantar psoriasis warrants much further research.

Combination treatment. Studies combining biologics with traditional systemic agents in different dosage schedules compared with biologic agent monotherapy or systemic agent monotherapy are needed to optimize clinical efficacy and cost reductions of therapy, while minimizing side effects over the long term. Methotrexate is often used in combination with biologic therapies as this is considered to produce a synergistic or additive effect and because it may increase the duration of sustained response by reducing the development of antidrug antibodies. Well-designed studies are needed to validate this formally and to determine optimal dosage regimens in psoriasis treatment. Treatment algorithms of suggested combination therapy regimens based on clinical studies and expert opinion are needed to guide clinical dermatologists in difficult cases.

Future therapeutic pathways to be explored. An increased understanding of the complex immunopathogenesis of psoriasis has facilitated the development of several new, more selective biologic agents. The critical role of the Th17/IL-23 axis in the development of psoriasis has prompted the development of antibodies and receptor antagonists targeting IL-17, IL-22, IL-23, and their receptors. Other agents targeting different aspects of the inflammatory cascade, including Janus kinase inhibitors, protein kinase inhibitors, chemokine receptor inhibitors of cell adhesion molecules, antiangiogenic therapies, and the sirtuin pathway are also being evaluated. The discovery of new cellular and molecular pathways important in disease pathogenesis will allow the identification of novel therapeutic targets. Further research, education, and strategies to improve patient adherence to current treatment regimens, however, may be more valuable and more cost-effective than the development of new treatments.

Secondary failure to treatment. Our understanding of the mechanisms governing secondary treatment failure to previously effective treatments remains poor. A significant proportion of patients who have achieved a favorable response to biologic treatments gradually lose response over time and many patients who recommence a previously effective treatment fail to achieve a similar level of response when reinitiated on the drug. This can be attributed in part to the development of neutralizing antidrug antibodies. Patients with psoriasis who develop antidrug antibodies to monoclonal antibodies such as infliximab and adalimumab resulting in lower serum levels of the drug are less likely to respond to these drugs but patients do not appear to develop antidrug antibodies to etanercept. Studies to determine the optimal drug dosing, treatment schedule, and concomitant medications required to minimize
antidrug antibody formation are needed to prevent the development of immunogenicity to highly efficacious treatments. The monitoring of drug levels and antidrug antibodies may be useful to inform the development of immunogenicity to a biologic treatment and the need for a change in the treatment regimen. Other epigenetic, environmental, and metabolic factors contributing to secondary treatment failure to psoriasis treatments must be further elucidated. This will also be useful in designing treatment regimens to minimize these effects.

**Treatment goals.** The majority of patients with objectively severe psoriasis are treated with topical agents alone. More data are required to determine the patient, physician, treatment, and economic factors that result in patients with severe disease not achieving long-term control of their psoriasis. More research is needed to determine what the majority of patients now view as an adequate or optimal response. With increasing efficacy of new treatments, 90% reduction in Psoriasis Area and Severity Index score may become the measure of optimal response rather than 75% reduction in Psoriasis Area and Severity Index score. More research is needed to ensure that patients are satisfied with management of all aspects of their disease and that we fully understand their needs. The definition of treatment goals and the development of simple, practical treatment algorithms suitable for dermatologists in routine clinical practice can ensure that measures are taken to improve treatment outcomes when these goals are not met.

**Personalized medicine**

The science of personalized medicine is gaining momentum across all spheres of medicine and there is a great need for biomarkers to predict treatment outcomes and individualize care for patients with psoriasis. Pharmacogenetic studies in psoriasis have used single nucleotide polymorphisms to predict treatment response to methotrexate, acitretin, and TNF-alfa inhibitors. These studies were retrospective, had limited power, and did not use objective measures of treatment response. Dissecting the relationship between genetic variability and treatment response is challenging, however, and genetic polymorphisms alone are not sufficient to explain variability in clinical response as many patients lose response to previously effective treatments. Smaller studies have used microarray technology to identify transcriptional signatures predictive of treatment response to alefacept before treatment initiation or during the early stages of treatment. The use of drug level monitoring and measuring antidrug antibody levels in early treatment may help to predict treatment response early in therapy. The analysis of potential biomarkers of treatment response as part of drug registries or large-scale clinical drug trials could facilitate advances for personalized medicine in psoriasis. Biostatistical data-modeling techniques that correlate treatment response with serum drug levels and potential biomarkers gleaned from pharmacogenetic studies, gene expression profiling, and epigenetic, flow cytometric, proteomic, and metabolomic studies need to be developed.

**Safety**

There is a lack of long-term safety data for both well-established and newer treatments in patients with psoriasis. Much of our safety data are extrapolated from other diseases, particularly the RA population, but it is unclear if such data accurately reflect the safety of these agents in patients with psoriasis. For example, large meta-analyses showed no increase in serious infections and cancer in RCTs of patients with psoriasis treated with TNF-alfa inhibitors in contrast to findings in patients with RA. This may be because TNF-alfa inhibitors are typically administered as monotherapy in psoriasis studies, whereas in RA they are often combined with other immunosuppressants that may alter the safety profile. Our long-term experience of newer, targeted biologic treatments is limited and the relatively short time period of the placebo-controlled phases of RCTs greatly hinders our ability to make conclusions with regard to safety, particularly for rare or long-term adverse effects. It is critical that short-term (12 weeks) and intermediate-term (52 weeks) studies, currently the gold standard for psoriasis phase II and III studies, respectively, be augmented by longer-term studies of 3 to 5 years. This would allow the detection of rare side effects, such as MACE and serious infections (eg, progressive multifocal leukoencephalopathy) or potentially beneficial effects, including reduction in cardiovascular morbidity or prevention of the development of PsA. Phased approval by drug regulatory agencies, mandating the continued collection of comprehensive safety data in postmarketing and observational studies, is a potential means of addressing this need. The use of drug registries with clearly defined objectives is essential to monitor the long-term safety of new agents under development. Unfortunately, the majority of registries in the United States are funded by the pharmaceutical industry and generally not inclusive of patients being treated with therapies manufactured by other pharmaceutical companies. In Europe, national and international registries of all patients with psoriasis being treated with systemic
agents have been developed and it is important that similar registries are developed in the United States. Results of predetermined outcome measures from these registries should be relayed at regular intervals.

**Health care economics**

Cost considerations are vitally important in this era of limited resources and budget deficits in health care. Determining the cost of psoriasis and its associated comorbidities should encompass the cumulative cost of psoriasis to the patient, to the health care system, and to society in general. Development of better clinical outcome measures to measure the global burden of disease with regard to clinical severity, symptoms, quality of life, and quality of care is essential. The cost-effectiveness of short- and long-term therapies for a chronic, lifelong disease such as psoriasis must be evaluated so these treatments can be fully accepted by national health services, medical insurance companies, and third-party payors. Comparative cost-effectiveness studies are also needed to inform clinical decision-making. Increasingly, cost-utility analyses will be needed to quantify the psychosocial burden of disease so we can incorporate quality-of-life measures into treatment decisions. Much further research is needed in this area of psoriasis management (Table VII).

Another important area in health care economics is health care delivery. Further research is needed to develop models to integrate primary care physicians, physician assistants, and clinical nurse specialists into psoriasis management programs, particularly with regard to education and training for optimal treatment of patients with psoriasis. Safe prescribing of systemic and biological therapies by physician assistants and nurse specialists requires good infrastructure and specialist training, encompassing patient screening, patient education, prescription coordination, patient support, and monitoring. The benefits of moving to nurse-led treatment of psoriasis have been suggested in other countries but further research is needed to determine their use in the US health system. Teledermatology is now a growing field across all of dermatology. Several studies have examined the use of teledermatology in the home monitoring of psoriasis in patients treated with biologic agents, and shown it to be safe and acceptable to both patients and dermatologists, with fewer visits to dermatology offices allowing improved quality of life to patients in remote areas. Further larger studies are needed to validate these findings and to further evaluate the potential role of this technology in psoriasis management.

**CONCLUSION**

The future for patients with psoriasis is very promising. The past decade has seen fundamental paradigm shifts in the understanding of psoriasis pathogenesis, leading to a dramatic growth in our therapeutic armamentarium. Many new selective agents are currently in development or under investigation. The ultimate “cure” of psoriasis, however, is still many years away. This will most likely involve gene therapy or modulation of the immune response to factors initiating and maintaining the disease. Key research priorities include further delineation of the molecular pathways of psoriasis and PsA to identify novel therapeutic targets; identification of the function of psoriasis susceptibility genes to investigate phenotype-genotype relationships and completing the genetic map of psoriasis; development of robust, long-term, prospective population epidemiology studies to determine the prevalence and natural history of psoriasis in various ethnic groups; and examination of the role of environmental factors in the development and exacerbation of psoriasis. Further studies are also necessary to identify biomarkers of disease severity and treatment response, to evaluate psychological interventions as adjunctive therapy in appropriate patient groups, and to further investigate the relationship of psoriasis

**Table VII. Proposed studies to address research gaps in health care economics in psoriasis**

<table>
<thead>
<tr>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Studies to determine the patient, physician, treatment, and economic factors that result in a significant proportion of patients with psoriasis and severe disease not achieving long-term control of their psoriasis</td>
</tr>
<tr>
<td>2. Studies to determine what patients with psoriasis view to be an adequate or optimal response</td>
</tr>
<tr>
<td>3. Studies to examine if patients are satisfied with management of all aspects of their disease so that we fully understand their needs</td>
</tr>
<tr>
<td>4. Studies to evaluate individualized therapy for patients with psoriasis; the analysis of potential biomarkers of treatment response in drug registries or as part of large-scale clinical trials could facilitate great advances in the field of personalized medicine</td>
</tr>
<tr>
<td>5. Studies to develop better clinical outcome measures for the measurement of the global burden of disease with regard to clinical severity, symptoms, quality of life, and quality of care</td>
</tr>
</tbody>
</table>
with its associated cardiovascular comorbidities. Data sharing and the rapid dissemination of new findings between research groups will be essential to facilitate further advances in psoriasis research at a global level. Despite revolutionary advances in psoriasis therapy, our long-term experience of newer targeted treatments is still limited and robust evidence of long-term safety data is essential to safeguard our patients. To this end, it is critical that dermatologists become actively involved in accruing these data by enrolling patients in drug registries and continuing to report adverse events and safety concerns at the earliest stage.

Dr Ryan was a speaker for Janssen-Cilag and Pfizer receiving honoraria, served on the advisory board for Galderma and Abbott receiving honoraria, and in another role with Abbott she has received a research fellowship and additional funding. Dr Korman has served on the advisory board and was investigator for Colgene, Eli Lilly and Pfizer for which he received honoraria and grants; he has also served on the advisory board for Novartis where he received honoraria; in his role with Janssen he has served as advisor, investigator and speaker receiving grants, funding and honoraria; he has also served as an investigator for Genentech and a consultant for Astellas receiving grants and honoraria for each and speaker for Genentech and Astellas receiving grants and honoraria. Dr Gelfand served as consultant and investigator with Amgen, Abbvie, and Lilly receiving grants and honoraria; has consulted for Pfizer, Janssen, Celgene, and Merck receiving honoraria; and investigated with Norvatis, and Genetech, receiving grants. Dr Gelfand is supported by NIH/NIAMS grant K24AR064310. Dr Lim disclosed no relevant conflicts of interest. Dr Elmett served as an investigator for Abbott and Amgen for which he received grant support, his consulting relationships with Ferndale Lab and Vaxin have provided honoraria and stock options, he has received no compensation for his consulting relationship with Brickell, he serves on the advisory board for Leo Pharma and has other roles with Astellas for which he receives fees. He is a shareholder in Palomar for which he receives stock options. Dr Feldman serves as a consultant, investigator and speaker for Taro. He has received grant support from National Psoriasis Foundation, Aventis Pharmaceuticals, Ortho Pharmaceuticals, and Roche Dermatology. For 3M he served as a speaker and received grant support. He received research grants from the Dermatology Foundation, American Society for Dermatologic Surgery, and the American Acne Rosacea Society and Medicis. For Medicis he also served as a consultant. For Coria/Healthpoint/Vaean and Pharmaderm/Nycomed he served as a consultant for which he received grant support.

Galderma, Stiefel/GSK, Astellas, Abbott Labs, Centocor, Amgen and Warner-Chilcott, Bristol-Myers Squibb Dermatology supported Dr Feldman’s role as speaker and consultant with grants. Dr Feldman receives stock options and research support for his role at Photomedex. Novartis provides research support for his consulting and speaking. He serves as a consultant for Leo/Peplin for which he receives grant support. Dr Feldman serves as a consultant for Caremark, Hanall Pharma, Kikaku, Medscape, Suncare Research, and Merck. He has also received royalties from Informa and Xlibris. Dr Feldman is the founder and Chief Technology Officer for Causa Research, in addition to being a stock holder, and is a majority stock holder for Medical Quality Enhancement Corporation. He received separate department funding from Acuderm, Advanced Tissue Sciences, Allergan, Aventis, Bristol-Myers Squibb, Combe, Curatek, Ferndale, Fujisawa, Hermal, Hoffman LaRoche, Galderma, Gennerr, Glaxo Wellcome, Hill, Janssen, Mayrand, Neoskrata, Neutrogena, Novartis, Oclussen, Ortho, Person & Covy, Proctor & Gamble, RJR Nabisco, Schering-Plough, Shelton, SmithKline, Stiefel, 3M, United Catalyst, Upjohn, and Wolff Systems. Dr Gottlieb maintains current consulting/Advisory Board agreements with Amgen Inc, Astellas, Centocor (Janssen), Celgene Corp, Bristol Myers Squipp Co, Beiersdorff, Inc, Abbott Labs (Abbvie), TEVA, Actelion, UCB, Novo Nordisk, Novartis, Dermipos Ltd, Incyte, Pfizer, Canfit, Lilly, Coronaon, Vertex, Karyopharm. Tufts Medical Center received Research/Educational Grants from Centocor (Janssen), Amgen, Abbott (Abbvie), Novartis, Celgene, Pfizer, and Lilly for Dr Gottlieb’s efforts. Dr Koo serves as a speaker for Leo and Abbvie, for which he receives honoraria. He fulfills the role of investigator for Amgen, Novartis, Merck, Janssen and Photomedex, receiving grants. Dr Lebwohl serves as a consultant for Abbott, Anacor Pharmaceuticals, Inc, BioLineRX, Ltd, Coronado Biosciences, Dermiposr, Galderma, Maruho Co Ltd, Novartis, Pfizer, and Valeant, for which he received honoraria and other compensation. In his role as consultant and investigator for Amgen, Celgene Corporation, Eli Lilly & Co, Jassen Ortho Biotech, and LEO Pharmaceuticals, he receives grants and honoraria. GlaxoSmithKline-Stiefel provides Dr Lebwohl with an honoraria for his work as an investigator and he receives grants and honoraria from Ranbaxy as an investigator and lecturer. Honoraria from Galderma were donated directly to charity. Members of Dr Lebwohl’s department own patents on short-contact tazarotene, topical genistein, and use of the excimer laser for vitiligo. Dr Lebwohl serves as principal investigator for Can-Fite Biopharma Ltd and Centocor. Members of Dr Lebwohl’s department serve as investigators for numerous companies including Abbott, Actavis, Amgen, aRigen, Astellas, Basilea, Bayer/Intendis, Bioform, Can-Fite Biopharma., Celgene, Centocor, Dusa, Eli Lilly, Ferndale, Fougera Pharmaceuticals, Galderma, Genentech, Graceway, Lumenis, Medicis, Merck/Schering Plough, Merz, Novartis, Nycomed, Onset Therapeutics, Peplin, Pfizer, Proventus, Ranbaxy, Regeneron, Stiefel, Valeant, Vascular Biogenics, and Wyeth. Dr Lebwohl is a course director for
the annual Fall and Winter Clinical Dermatology Conferences and the annual Mount Sinai Winter Symposium, which receive support from numerous dermatology companies. Dr Leonardi is speaker, consultant, investigator and enjoys a place on the advisory board for Abbott, Amgen and Janssen. He serves on the advisory board and as an investigator for Eli Lilly and Celgene, receiving honoraria and other financial benefit. He served as investigator for Anacor, Galderma, Glaxo Smith Kline, Incyte, Maruho, Novartis, Nordisk, Pfizer, Schering Plough, Sirtris, Stiefel, Vascular Biogenics, Warner Chilcott, and Wyeth, for which he receives other financial benefit. Dr Van Voorhees served on the Advisory Board and was an investigator, speaker, and consultant for Amgen, receiving grants and honoraria; was a member, and speaker for Abbott receiving honoraria; she sits on the advisory board for Genentech, Warner Chilcott, Leo and Novartis, receiving honoraria; and she received honoraria for her participation on the advisory board and for her role as a speaker for Janssen. Dr Bhushan had no relevant conflicts of interest to disclose. Dr Menter served on the Advisory Board and was a consultant, investigator for Abbott Labs, Amgen, Astellas, Genentech, Janssen and Wyeth, receiving grants and honoraria; was a consultant and investigator for Eli Lilly and Stiefel, receiving honoraria and grants; and he served as investigator for Allergan, Celgene, Novartis, Pfizer and Syntx Biosystems, receiving a grant from each. He received honoraria from LEO Pharma for consulting and speaking. He serves on the advisory board, speaks, and consults for Galderma, for which he received honoraria.

REFERENCES


167. Cole PD, Zebala JA, Alcaraz MJ, Smith AK, Tan J, Kamen BA. Pharmacodynamic properties of methotrexate and...
Aminopteran during weekly therapy. Cancer Chemother Pharmacol 2006;57:826-34.


