Clinical review

Psoriasis and its management

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BMJ 2006;333:380–4

Behcet (1935) referred to the highly stigmatising and common inflammatory skin disease psoriasis (derived from the Greek word psora meaning itch) as "the antidote to a dermatologist's ego," and although in some respects this is still true, major progress has been made in several important areas. Psoriasis occurs worldwide and affects about 2% of the population in the United Kingdom.

A great deal is known about the genetic and immunological mechanisms underlying the pathogenesis of psoriasis. Some of the new biological treatments recently licensed for psoriasis have been developed as a result of this improved understanding, whereas others have been contributory—for example, the profound efficacy of agents that block the actions of cytokine tumour necrosis factor highlighted the key role of tumour necrosis factor in the disease's pathogenesis. Evidence is also accumulating that psoriasis is not just associated with skin disease. Epidemiological studies have shown an increased standardised mortality in patients with psoriasis, particularly related to cancer and heart disease. Clinically relevant psychological and psychiatric comorbidity are also common and potentially amenable to therapeutic intervention. This article presents an overview of these developments and their implications for clinical practice.

Summary points

- Psoriasis is a common, disfiguring, and stigmatising skin disease associated with profound impaired quality of life
- The gene locus PSORS-1 is the major determinant of psoriasis, and identification of the specific gene is imminent
- Cardiovascular disease and some cancers (particularly skin cancer after excessive photochemotherapy) are more common in patients with psoriasis, especially those with more severe disease
- Anxiety and depression affects up to 25% of patients with psoriasis, and is often missed in clinical practice
- Most patients presenting in primary care can be managed with topical therapy alone
- Recently licensed biological treatments (efalizumab, etanercept, infliximab) provide a major advance in treatment but are currently indicated only for limited severe disease owing to lack of data on long term safety and efficacy, and cost

What causes psoriasis?

Genetic factors

Scans of the human genome reveal at least nine different loci with susceptibility to psoriasis (PSORS1-9). PSORS-1, a region of the major histocompatibility complex on chromosome 6p2, is the major genetic determinant of psoriasis, and accounts for up to 50% of genetic susceptibility to the disease,[1 w1] although the definitive gene has not yet been identified.

Several of the implicated loci are shared by other autoimmune and inflammatory diseases such as inflammatory bowel disease, type1 diabetes, multiple sclerosis, and atopic dermatitis, suggesting that similar mechanisms underlie many common genetically complex inflammatory diseases.

Immunological and environmental factors

Evidence is emerging that both innate (non-adaptive immunity that represents phylogenetically ancient, broad spectrum mechanisms that are not specific to antigens) and acquired (antigen specific) immune mechanisms are altered in clinically uninvolved skin.[1 2 w2]

In this environment key primary cytokines (for example, tumour necrosis factor α and interferon α) are released, perhaps as a result of environmental triggers, including infection, drugs, trauma, and stress.[2 3] This hypothesis is supported by the profound efficacy of agents that block the actions of tumour necrosis factor α, such as infliximab,[4] and the therapeutic potential of agents that interfere with pathways linking innate and acquired immunity.[w3]

P+ *A table of treatments and references w1-w24 are on bmj.com*

Sources and selection criteria

We searched the Cochrane database of systematic reviews, the United Kingdom's health service health technology assessment programme, Embase, and Medline for systematic reviews and randomised trials between 1995 and to 2006 using the broad terms "psoriasis" and "treatment". We used systematic reviews as source data, when relevant, owing to the size of the topic; additional evidence cited includes data from large randomised controlled trials when these are not included in systematic reviews, published consensus statements, evidence based reports issued from the UK Department of Health, and additional ad hoc material known to the authors.

How is psoriasis diagnosed?

Psoriasis is diagnosed on the basis of clinical findings (skin rash, changes to nails, joint involvement) and is usually straightforward. Occasionally patients present with atypical skin lesions that need to be differentiated from tinea, mycosis fungoides, discoid lupus, or seborrhoiec dermatitis, or non-specific skin signs such as minimal scaling of the scalp, isolated flexural erythema, or genital lesions. Careful assessment of all body sites may reveal undeclared, diagnostically useful features, and a skin biopsy may occasionally be indicated. Chronic plaque psoriasis (psoriasis vulgaris, figs 1 and 2) is by far the most common type, but other morphological variants include guttate psoriasis, flexural or "inverse" forms (body folds), sebopsoriasis, erythrodermic psoriasis (total body redness and scaling), and pustular psoriasis (localised or generalised palmar plantar disease). Occasionally combinations of the different types develop simultaneously or sequentially over time in the same patient.

What is the clinical effect of psoriasis?

Psychosocial effect

As a result of the chronic, incurable nature of psoriasis, associated morbidity is significant. Patients in primary care[5] and hospital settings have similar reductions in quality of life, comparable to those reported for major diseases such as cancer, heart disease, and diabetes.[6–8] Diminutions in quality of life encompass functional, psychological, and social dimensions. Symptoms specifically related to the skin (for example, chronic itch, bleeding, scaling, nail involvement), [w4] problems related to treatments (mess, odour, inconvenience, time), arthritis, and the effect of living with a highly visible, disfiguring skin disease (difficulties with relationships, difficulties with securing employment, and poor self esteem) all contribute to morbidity.[7 w5] Even those with minimal involvement (less than the equivalent of three palm areas) state that psoriasis has a major effect on their life.[9 w5 w6]

About one in four patients experience major psychological distress, and the extent to which they feel socially stigmatised and excluded is significant. Doctors, including dermatologists, often fail to appreciate the extent of this disability[6] and even when it is correctly identified, fewer than a third of patients receive appropriate psychological interventions. Such factors may affect treatment outcome,[6] but they are potentially amenable to intervention. In one study the addition of cognitive behavioural therapy to standard treatment led to significantly greater reductions in anxiety and depression, in self reported disability and stress, and in objective clinical severity of psoriasis.[w7]

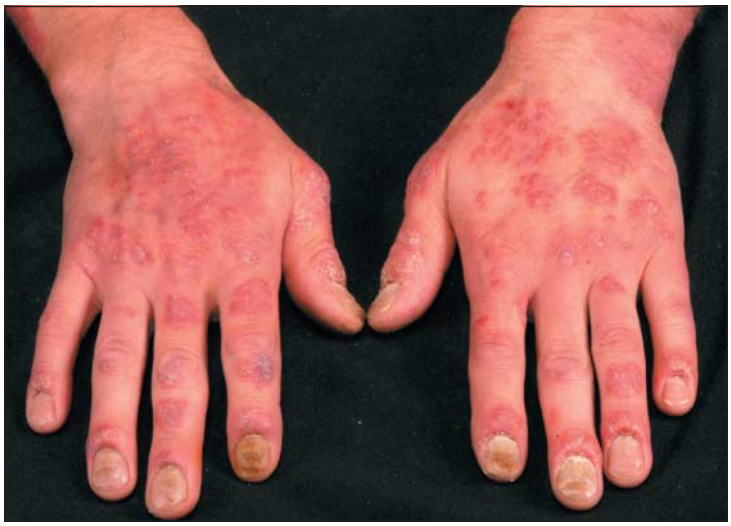

Fig 1 Plaques show varying degrees of scaling, thickening (induration), and inflammation (redness) are typically oval shaped, of variable size (from less than 1 cm upwards), and clearly distinct from adjacent normal skin. Characteristic nail changes include pitting (shown), onycholysis, and subungual hyperkeratosis

Associated comorbidity: cardiovascular disease and cancer

Patients with severe disease seem to have at least a two-fold or threefold increase in mortality from cardiovascular disease.[10 w8] Several potentially inter-related factors are likely to contribute to this risk (box 1). Several community and hospital based studies have shown an increased risk for a variety of malignancies,[11–13 w9] and in patients with severe disease the risk seems to be comparable to that of patients after organ transplantation, with significant increases documented for lymphoma and non-melanoma skin cancer. The relative influence of known confounders such as concomitant therapy with immunosuppressants and phototherapy,[w9 w10] smoking, and alcohol[14] is not yet clear.

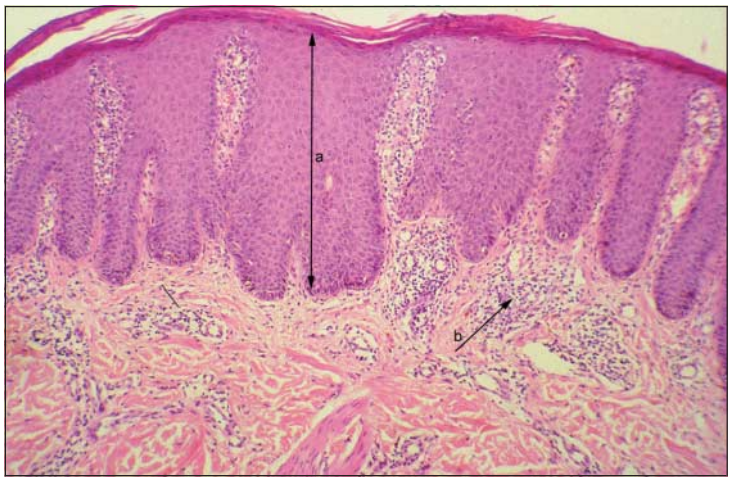

Fig 2 Histologically, psoriasis is characterised by epidermal thickening (arrow a) as a result of proliferation and impaired maturation of keratinocytes (normal cycle of keratinocyte maturation is 28-30 days whereas in psoriatic plaques this accelerates to three or four days), leucocyte infiltration (arrow b), and new blood vessel formation (angiogenesis)

Box 1 Risk factors for cardiovascular disease in patients with psoriasis

Obesity
The prevalence of obesity is double that of the normal population and those with other types of skin disease; weight gain occurs after disease onset and is related to a sedentary lifestyle [15]

Smoking
The risk of psoriasis is higher in smokers (relative risk 1.7) and former smokers (1.9) than never smokers, with high consumption (≥ 20/day) and long duration of smoking particularly related to severe disease in women[15]

Alcohol
Patients with psoriasis show high rates of excess alcohol intake, alcoholism, and death due to alcohol related diseases[14]

"Stress"
"Stress" may be more common in patients with psoriasis; widely believed by patients to be a cause or trigger of psoriasis and flare ups[6]

Hyperlipidaemia
Increased rates of hyperlipidaemia occur in patients with severe, longstanding disease[w11]; partly iatrogenic due to prolipidogenic effects of antipsoriatic treatments (ciclosporin, acitretin)

Chronic inflammation
Chronic inflammation is a recognised risk factor in other diseases such as rheumatoid arthritis and systemic lupus erythematosus and may also be relevant in psoriasis[w12]

What are the management options for patients with psoriasis?

For those who request active intervention (not all will) the main aim is to reduce disease activity to a level that allows an acceptable quality of life with minimal toxicity from treatment. Antibiotics and tonsillectomy have often been advocated for patients with recurrent guttate psoriasis or chronic plaque psoriasis, but good evidence is lacking for either intervention being beneficial.[16 17] Interventions comprise topical therapy, phototherapy, systemic (predominantly immunosuppressant) agents (see bmj.com), and biological treatments.

Topical therapy

Adherence to topical therapy regimens is poor, and even when patients are told that drug use is monitored (in clinical trials through electronic bottle caps), treatment is adhered to just over half the time.[w13] Concordance in clinical practice is likely to be much lower but can be improved when attention is given to cosmetic acceptability, local side effect profiles, formulation, and practicalities of application. Nurses with dermatological training (particularly given the introduction of the extended nurse prescribing formulary in the United Kingdom) are ideally placed to fulfil this role, and some evidence supports this approach.[w14] Nurse led outpatient treatment centres are key sources of psychological support and advice for patients and also facilitate combining topical therapy with phototherapy.

Therapeutically active topical agents licensed for psoriasis include corticosteroids, vitamin D analogues, tar, dithranol, and tazarotene (a retinoid). A recent systematic review[18] concluded that in the short term active treatment conferred significant benefit over vehicle (around a two point improvement on a 12 point total severity score after six to eight weeks), with no noticeable differences in magnitude of benefit between the different classes of drugs, with the exception of very potent corticosteroids (greatest effect). Comparison of agents in head to head studies indicated that vitamin D analogues were of similar efficacy to potent corticosteroids and more effective than dithranol (fewer reported adverse effects). Of the three vitamin D derivatives currently available, calcipotriol is marginally more effective than tacalcitol or calcitriol[19] and, when combined with a potent or very potent steroid, more effective than calcipotriol alone.[19]

In practice topical corticosteroids (potent and, less commonly, very potent) are widely used since they are effective and onset of action is rapid. Mild strength corticosteroids or, provided it is for limited periods only, moderate strength corticosteroids can be used for facial and flexural disease. Intermittent use (twice weekly or at weekends)[18] or use combined with non-steroidal agents (for example, calcipotriol)[18] may maintain remission while minimising risks that can occur with continuous use, such as loss of efficacy, cutaneous atrophy, and rebound or pustular psoriasis.[w15] The vitamin D analogues are also widely used, but although efficacy is comparable to that of potent corticosteroids without the attendant risks, onset of action is slow and skin irritation common (about 20%-25% of users), hence the utility of combination therapy with corticosteroids that tends to abrogate both these problems. The calcineurin inhibitors tacrolimus (1%) and pimecrolimus are prescribed occasionally for difficult flexural or facial psoriasis,[w16 w17] although no good evidence exists for size of benefit.

Phototherapy and systemic treatments

Firm, short term evidence on the efficacy of phototherapy—ultraviolet B light and photochemotherapy (psoralen plus ultraviolet A light, PUVA)—and most of the systemic treatments for psoriasis (see bmj.com) come from randomised controlled trials, but few comparative studies have examined the relative efficacy and safety of the different interventions.[20 21] Those that do have failed to address clinically important questions such as duration of remission when treatment is stopped or whether efficacy is maintained with continuous or intermittent use. Strategies to reduce toxicity from long term treatment include rotational or sequential use of systemic therapy, drug holidays, and combination therapy. Tertiary centres with access to multidisciplinary teams with experience in multiple drug therapies provide specialist care for the minority of patients with severe, recalcitrant disease.

What's new in secondary care?

Phototherapy

In many centres conventional broad band ultraviolet B light (emission spectrum 270-350 nm) has been largely superseded by the newer, more effective, narrow band ultraviolet B light (311-313 nm) through the TL-01

A patient's perspective

My psoriasis erupted, covering my entire body with painful lesions. Not only was this agonising to the touch but it also discouraged mobility. I remember fixating myself into a crouching position, avoiding any movement that might cause my skin to break. I was tried on a course of light treatment, but the management of my care relied heavily on an intensive regimen of emollients; this proved to be time consuming and messy, often staining bed linen, clothing, and anything else I came into contact with. I was routinely bathed, creamed, and tarred, then mummified with cling film and bandages twice daily; this made for many sleepless nights writhing under the rustling cellophane that cocooned the squelching mass of ointments and sweat . . . My first encounter with an arthritic condition associated with psoriasis flared up during my adolescence, and again with much greater severity when I turned twenty . . . I am unable to describe the pain I suffered, only to say without embellishment that my life henceforth to be overwhelmed by it. Any resolve I may have once held had long since diminished, my frailties surfaced, and in such a contemptible state of being I resigned myself to despair and abandoned hope. Tried on countless medications (topical and systemic), which have not only proved ineffective but also given rise to some very unpleasant side effects . . .

lamp (Philips Lighting, Netherlands).[w18] The traditional hierarchy of treatment toxicity, when PUVA is perceived to be safer than systemic agents such as ciclosporin and methotrexate, may be changing also, especially when considering treatments in young people.

Also changing is the practice of proceeding to systemic treatments only when total cumulative dose exceeds recommended levels. This is because the inherent risks of skin cancer in association with PUVA[w19] are also substantially increased when ciclosporin is used.

Drug monitoring

Methotrexate is still considered the ideal therapy for moderate to severe psoriasis, especially if arthritis or nail involvement is present, since it is highly effective over protracted periods (50% reduction in disease severity in 75% of patients[20 21]). Clinicians and patients have been discouraged from using methotrexate, however, because of the need for routine liver biopsies to detect, albeit rare, clinically and biochemically silent liver fibrosis and cirrhosis. Recently, measurement of serum procollagen III (every three months during treatment) has been adopted as a surrogate marker of liver toxicity and means that most patients can avoid liver biopsies.[22 23 w20]

Systemic drugs for psoriasis pose a risk, but those specifically related to methotrexate were highlighted by the National Patient Safety Alert in 2004, including the need to closely monitor patients; make explicit where responsibility for this lies; and provide adequate, appropriate, and consistent information to all those involved in care (including the patient).[w21] Implementation of the recommendations required important changes in the detail and logistics of prescribing for methotrexate (including mandatory patient held records), but the process is of relevance and value to all drug prescribing.

Biological treatments

Biological treatments are agents that block molecular steps important in the pathogenesis of psoriasis. They have emerged over the past five years as valuable alternative therapeutic options for psoriasis. Currently they comprise two main groups: agents that target the cytokine tumour necrosis factor α (for example, etanercept, infliximab, adalimumab) and agents that target T cells or antigen presenting cells (for example, efalizumab). Despite the need for parenteral administration (intravenously every eight weeks for infliximab, self administered subcutaneous injections twice weekly, weekly, or every two weeks for the others), widespread dissatisfaction of patients with standard treatments[9] has led to high demand. Their role in the context of existing standard systemic therapies is limited at the moment, given the relative lack of data on long term safety and efficacy,[24] but undoubtedly for some patients with severe disease these treatments can be life saving. Risks of infection (especially tuberculosis with the antitumour necrosis factor agents) and possible future malignancy remain concerns. Availability of biological treatments in the United Kingdom is highly restricted at present, but this may change following recent approval (July 2006) by the National Institute for Health and Clinical Excellence for use of etanercept and efalizumab in severe psoriasis provided certain qualifying criteria are met.

Who should be treating psoriasis and where?

Most patients with confirmed psoriasis should be able to self manage their condition with appropriate, probably nurse led, readily accessible support.[w14 w22] Box 2 suggests indications for specialist referral. At some point referral might be required in up to 30% of primary care patients, although who provides this and where will depend on the configuration of local services. The past five years, since 2000, has seen major expansion in dermatology specialist outreach schemes (schemes involving specialists providing care in the

Box 2 Indications for referral to secondary or intermediary care for psoriasis as suggested by the Primary Care Dermatology Society and British Association of Dermatologists

Diagnostic uncertainty*

Request for further counselling or education, including demonstration of topical treatment

Failure to respond to appropriately used topical therapy for three months

Psoriasis at sites that are difficult to treat (scalp, face, palms, soles, genitals) if unresponsive to initial therapy

Adverse reactions to topical therapies

Need for systemic therapy,* phototherapy,* day treatment, or inpatient admission*

Disability preventing work or excessive time off work

Acute unstable psoriasis (urgent referral may be justified)*

Erythrodermic or generalised pustular psoriasis (emergency referral indicated)*

*Supervision by consultant dermatologist in whole or part required

Additional educational resources

Griffiths CEM, Camp RDR, Barker JNWN. Psoriasis. In: Burns T, Breatnach S, Cox N, Griffiths CEM, eds. *Rook's textbook of dermatology, vol 2*. 7th ed. Oxford: Blackwell Science, 2004.

British Association of Dermatologists (www.bad.org.uk/healthcare/guidelines/psoriasis.asp)—guidelines for psoriasis.

Henge UR, Ruzicka T, Schwartz RA, Cork MJ. Adverse effects of topical glucocorticosteroids. *J Am Acad Dermatol* 2006;54:1-15.

Alahlafi A, Burge S. What should undergraduate medical students know about psoriasis? Involving patients in curriculum development: modified Delphi technique. *BMJ* doi:10.1136/bmj.330.7492.633.

Information for patients

British Association of Dermatologists (www.bad.org.uk)—provides information about skin and skin diseases (including psoriasis), written and approved by UK practising dermatologists

Psoriasis Association (www.psoriasis-association.org.uk)—this UK based association is specifically for patients (and carers) with psoriasis. The site includes useful information, links to other sites, details of how to contact the association for telephone advice and support, and how to become a member

Psoriatic Arthropathy Alliance (www.paalliance.org)—this UK based organisation was founded by a patient with psoriasis. The site provides information on psoriatic arthritis as well as psoriasis and how to become a member

National Psoriasis Foundation (www.psoriasis.org)—this is a large, US based organisation for patients, and the website is comprehensive covering all aspects of the disease, useful links, and details of how to join the foundation

community) much of which has been prompted by the modernisation agenda in the NHS and the need to improve access to care for patients. The deficit in general practitioners' knowledge of skin disease is recognised as a major problem, but recent research suggests that this could in part be tackled by better, more patient focused undergraduate training.[w23] To date only one systematic evaluation has been undertaken on general practitioners with a special interest in dermatology service in primary care.[25] Although no significant differences in clinical outcome (as defined by a dermatology quality of life index) were observed compared with the hospital setting,[25] overall the general practitioner led service was more expensive[w24] and 10% of those seen by the service still required hospital input. This underlines the need to ensure that community led services are not developed at the expense of requisite, hospital based services for complex or unresponsive cases, and that providers in primary and secondary care collaborate closely to develop cost effective strategies for service provision.

Key areas of ongoing research

To identify principle pathogenic pathways in psoriasis

To determine the major factors that influence response to treatment and prognosis

To develop new therapies on the basis of recently identified basic molecular mechanisms

Contributors: CHS reviewed the literature and wrote the article. JNWNB wrote and reviewed the article.

Competing interests: CHS and JNWNB have received support for trials from Wyeth and Serono (manufacturers of biological treatments). CHS has acted as a consultant for Novartis. JNWNB has acted as a consultant for Schering Plough, Wyeth, Serono, and Novartis.

Funding: None.

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(Accepted 30 June 2006)