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Psoriasis

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ABSTRACT Psoriasis is a chronic, immune-mediated inflammatory skin disease affecting 1.3–2.2% of the UK population.[1] Most commonly, psoriasis is characterised by well-demarcated, red plaques with adherent scale with a predilection for the scalp and extensor surfaces of the limbs. However, the effects of psoriasis go far beyond a patient's skin and may result in a degree of disability and impaired quality of life similar to that of other major medical conditions, such as cancer and heart disease. First-line therapies for most patients are topical treatments such as topical corticosteroids and vitamin D analogues. For those with more severe or treatment-resistant disease, second- or third-line therapies include phototherapy, systemic therapies such as methotrexate and more recently biologic therapies such as tumour necrosis factor (TNF) inhibitors. These therapeutic modalities are proven to be highly effective; however, the potential for long-term toxicity needs to be considered. Aside from the visible skin disease, psoriasis is also increasingly recognised to have important systemic manifestations. Psoriatic arthritis has long been established as an associated condition and, more recently, it has emerged that psoriasis is also associated with an increased risk of inflammatory bowel disease, cardiovascular disease and the metabolic syndrome. Both National Institute for Health and Care Excellence (NICE)[2] and Scottish Intercollegiate Guidelines Network (SIGN)[3] have recently published guidelines for the assessment and management of psoriasis which highlight the need for regular assessment in order to detect the development of arthritis and the presence of other co-morbidities such as obesity, diabetes, dyslipidaemia and hypertension.

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DECLARATIONS OF INTERESTS Professor Burden is a consultant, lecturer and researcher for Abbvie, Janssen, Lilly, Novartis, Pfizer, Sandoz, and UCB Pharma.

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OVERVIEW

Introduction

Psoriasis is a common, chronic inflammatory skin disease affecting 1.3–2.2% of Western populations.[1] It is one of the most readily diagnosable skin diseases for the general physician, requiring no diagnostic tests (see www.dermnetnz.org for representative images). There is considerable variation in clinical presentation, some of which can be explained by known genetic heterogeneity. Psoriasis vulgaris, or chronic plaque psoriasis, is the most common form of the disease, making up 90% of cases.[2] It is characterised by well-demarcated red plaques covered in adherent silvery scales symmetrically affecting the extensor surfaces of the limbs and with a predilection for the scalp. Genome-wide association scans of individuals with psoriasis vulgaris have identified about 40 genetic loci that harbour susceptibility genes. Interestingly, these genes appear to cluster in several discrete biological pathways, in particular antigen processing (e.g. HLA-C, ERAP1), interleukin 23 signalling (e.g. IL23R, IL23A), type I interferon production (IFIH1, RNF114) and NF-κB signalling (NFKBIA, TNFAIP3), together suggesting important roles for adaptive and innate immune mechanisms.[4] The major genetic determinant in psoriasis vulgaris is HLA-Cw*0602, and this association is strongest in guttate psoriasis. Guttate psoriasis, usually seen in children and adolescents, describes the eruption over about a week of multiple small papules of psoriasis over the trunk and limbs, often following streptococcal pharyngitis. The eruption clears over a few months, but a substantial proportion of patients later develop chronic plaque psoriasis.

Other conditions that have been considered within the spectrum of psoriatic disease include localised and generalised pustular psoriasis. It is notable however that these conditions are not associated with HLA-C and their precise nosology awaits clarification. The most common form of localised pustular psoriasis is palmoplantar pustulosis. This is an indolent, chronic, pustular and hyperkeratotic inflammation restricted to the skin of the palms and soles, most commonly in middle-aged women, with a remarkably strong association with cigarette smoking. Generalised pustular psoriasis is

a rare and potentially life-threatening disease in which sterile non-follicular pustules develop on areas of red tender skin. In its most acute presentation there is associated fever, neutrophilia and elevated C-reactive protein (CRP), leading to a mistaken diagnosis of pyogenic infection. Very recently, mutations in an interleukin 1 family gene (IL36RN) have been identified in generalised pustular psoriasis, leading it to be considered with the periodic fever syndromes.

The effects of psoriasis go far beyond a patient's skin and may result in a degree of disability and impaired quality of life comparable with that of other major diseases, such as cancer, heart disease and depression. Furthermore, severe psoriasis is associated with an increased risk of conditions such as psoriatic arthritis, inflammatory bowel disease, depression, cardiovascular disease and the metabolic syndrome. A study of the risk of myocardial infarction (MI) in patients with psoriasis showed an increased adjusted relative risk for MI that varied with age. For example, it was shown that a 60-year-old patient with severe psoriasis has an adjusted relative risk of 1.36 for having a MI compared with a 60-year-old who does not have severe psoriasis.[5] With regard to the metabolic syndrome, it is estimated that over 30% of patients with psoriasis over the age of 40 meet criteria for the metabolic syndrome although this was not found to correlate with the severity of skin disease.[6]

Assessment of severity and referral

There is increasing clinical use of scores to quantify the severity of psoriasis over time. These scores are required by regulators in the UK to determine eligibility for biologic treatments, and in determining treatment response. The most widely used score to determine the biological severity of disease at a given time is the psoriasis area and severity index (PASI), which rates the average redness, thickness and scaling of plaques, weighted by the area of involvement. A score of ten or more is considered severe disease. This score is only applicable in psoriasis vulgaris and so in other forms of the disease the affected body surface area (BSA) can be substituted. Taking 1% of BSA to be equivalent to the area of an outstretched hand including fingers and thumb, a patient with psoriasis affecting >10% of their BSA would be defined as having severe disease.

Assessment of severity of psoriasis should not be solely based on physician assessments but must also take into account the effect of psoriasis on health-related quality of life. In clinical practice this is usually quantified using the Dermatology Life Quality Index (DLQI). This is a validated ten-point questionnaire (www.dermatology.org.uk) and a score of 10/30 or more is considered severe disease. Thus severe psoriasis can be defined as a score of ten or more in either PASI, DLQI or BSA ('rule of tens'). The National Institute for Health and Care Excellence (NICE) and the Scottish Medicines Consortium (SMC) require PASI and DLQI to be ten or more to qualify for biologic treatment of psoriasis. The minimum response criteria on treatment are either a 75% reduction in PASI, or a 50% reduction in PASI with a five-point reduction in DLQI (Figure 1).

- Diagnostic uncertainty
- Any type of psoriasis that is severe or extensive
- Psoriasis not controlled with topical therapies
- Acute guttate psoriasis requiring phototherapy
- Nail disease with a major functional or cosmetic impact
- Psoriasis which is having a major impact on a patients' physical, psychological or social wellbeing

FIGURE 1 NICE guidelines for referring patients assessed in non-specialist setting for dermatology specialist advice.

Co-morbidities

Of particular relevance to the general physician is advancing knowledge of the co-morbidities associated with psoriasis. Psoriasis has important systemic manifestations similar to that of other chronic inflammatory diseases such as rheumatoid arthritis, including cardiovascular disease and the metabolic syndrome.

Psoriatic arthritis

Psoriatic arthritis affects around 20% of patients with psoriasis and is generally under diagnosed. Several patterns of joint involvement have traditionally been recognised (distal arthritis, asymmetrical oligoarthritis, symmetrical polyarthritis, arthritis mutilans and spondyloarthritis) but these are now generally categorised as peripheral and axial psoriatic arthritis. Psoriatic arthritis is usually seronegative and distinctive clinical features include dactylitis (swelling of an entire digit) and enthesitis (inflammation at the insertion point of tendon or ligament in bone, often presenting as heel pain or tennis elbow). Validated classification criteria have been developed for use in rheumatology practice to differentiate psoriatic arthritis from other forms of seronegative spondyloarthritis (CASPAR criteria).

Although previously considered to be a relatively non-destructive form of arthritis it is now known that about half of those affected will develop erosive disease seen on X-ray over a two-year period. The NICE and SIGN recommend annual assessments for psoriatic arthritis in patients with psoriasis and that if psoriatic arthritis is suspected patients should be referred to a rheumatologist.

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Cardiovascular risk, the metabolic syndrome and venous thromboembolism

Increased prevalence of obesity (odds ratio [OR] 1.79), dyslipidaemia (OR 1.16), hypertension (OR 1.03), type two diabetes mellitus (OR 1.62), and tobacco use (OR 1.31) in those with severe psoriasis are all thought to contribute to increased cardiovascular risk. There is also evidence that severe psoriasis raises cardiovascular risk independent of these conventional risk factors. Scottish Intercollegiate Guideline Network recommends annual screening of patients with severe psoriasis or psoriatic arthritis to include body mass index (BMI), diabetes mellitus screening, blood pressure measurement and lipid profile as well as lifestyle advice. Psoriasis is also a risk factor for venous thromboembolism and this should be kept in mind when patients with psoriasis are admitted to hospital or undergo surgery.

MANAGEMENT

Topical therapies

For the majority of patients, topical therapies will be offered first-line (Table 1). However, if topical treatment alone is unlikely to adequately control psoriasis, such as in extensive disease or nail disease, second- or third-line treatment options such as phototherapy or systemic therapy may be offered at the same time as topical treatments. The major adverse effects of topical therapies relate to the long-term use of potent corticosteroids (skin atrophy, striae and the potential for psoriasis to become unstable) and NICE recommends four-week breaks between courses, never to use potent corticosteroids at any site for longer than eight weeks and to restrict the use of very potent corticosteroids at any site for more than four weeks.

While the majority of patients will be managed as outpatients, a minority with severe disease may require inpatient treatment. The most recent NICE guidelines recommend that inpatient treatment on a dermatology ward should be available for patients with severe psoriasis. Certain treatments, such as the use of crude coal tar, may require inpatient care because of their odour or cosmetic effects.

Phototherapy

When topical therapies fail to adequately control psoriasis, and particularly when psoriasis is extensive, phototherapy should be considered. Twenty five years ago this would usually have been photochemotherapy with psoralen and ultraviolet A (PUVA) but as the action spectrum for anti-psoriatic activity has now been determined to be approximately 311 nm, and in view of the known carcinogenicity of PUVA, narrow-band UVB (NBUVB) using this wavelength is now the preferred option. This is delivered in dermatology departments approximately three times weekly for about 20 treatments. Narrow-band UVB is highly effective at clearing psoriasis plaques but its usefulness is dependent on the duration of disease-free remission, which is usually many months and sometimes up to a year.

TABLE 1 Summary of Scottish Intercollegiate Guidelines Network guidelines for topical treatment of psoriasis

	Plaque psoriasis	Scalp	Nail	Flexural
First-line	Short-term intermittent use of a potent topical corticosteroid OR a combined potent steroid plus calcipotriol ointment is recommended to gain rapid improvement in plaque psoriasis. If longer term treatment is needed then topical treatment with a vitamin D analogue is recommended.	If thick scaling of the scalp is present then initial overnight application of salicylic acid, tar preparations or oil preparations (e.g. olive oil, coconut oil) to remove thick scale is recommended.	Generally refractory to topical treatment. Topical corticosteroids, salicylic acid, calcipotriol or tazarotene used alone or in combination may be considered.	Moderate potency topical corticosteroids are recommended for short-term use in facial and flexural psoriasis.
Second-line	If a vitamin D analogue is ineffective or not tolerated then short contact dithranol, coal tar solution, cream or lotion or tazarotene gel may be considered.	Short-term intermittent use of potent topical corticosteroids or a combination of a potent corticosteroid and a vitamin D analogue is recommended in scalp psoriasis.		If moderate potency topical corticosteroids are ineffective in facial and flexural psoriasis, then vitamin D analogues or tacrolimus ointment are recommended for intermittent use.

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The most common short-term adverse effect of NBUVB is erythema, the risk of which can be reduced by careful dosimetry. Long-term risks include photodamage and possible dose-related risk of skin cancer. The risks of PUVA are greater, with the main adverse effects being an increased risk of skin cancer (particularly squamous cell carcinoma, but also melanoma), photodamage and premature ageing of the skin. With regards to the risk of melanoma there is no convincing evidence that PUVA increases the risk of melanoma. Current evidence suggests that there is no association between NBUVB exposure alone and skin cancer. Therefore patients who do not respond to topical therapy should be offered NBUVB first and if there is no response PUVA may be considered. Furthermore, those who have undergone >200 whole-body PUVA treatments and/or >500 whole-body UVB treatments should be invited for an annual skin cancer screening review.

Systemic therapy

Methotrexate, ciclosporin and acitretin are licensed systemic therapies for psoriasis. While each of these drugs has evidence for its efficacy, the risks and benefits should be weighed up for individual patients. The efficacy and safety profiles of these treatments are varied and the most appropriate treatment for an individual will depend on many variables, including disease severity, the need for rapid remission as opposed to maintenance treatment and the presence of psoriatic arthritis (Table 2). Methotrexate for example, is recommended in the NICE and SIGN guidelines as first-line systemic treatment for patients with severe chronic plaque psoriasis, especially those with concomitant psoriatic arthritis. Notable risks include haematological toxicity and hepatic and pulmonary fibrosis. Ciclosporin is the first choice systemic drug for those who require rapid or short-term disease control, have palmoplantar pustulosis or are considering conception. There are significant associated toxicities with ciclosporin including nephrotoxicity, hypertension and immunosuppression with a consequent increased risk of infection and malignancy. The National Institute for Care and Excellence recommends that ciclosporin should not be used continuously for more than one year in psoriasis. Acitretin, a derivative of vitamin A, may be prescribed if methotrexate and ciclosporin are not appropriate or have failed, or in pustular forms of psoriasis. A major concern in the use of acitretin is long-lasting teratogenicity making it unsuitable for women who intend to become pregnant within two to three years of stopping treatment. There is increasing interest in the use of fumaric acid esters in psoriasis (and also multiple sclerosis). These oral agents have been licensed for use in several European countries for many years but not in the UK. Their principle side-effects are flushing, diarrhoea and mild lymphopenia. Scottish Intercollegiate Guidelines Network guidelines recommend that they be considered if other systemic agents are not suitable or effective.

Biologic therapy

As there are limitations with many of the above treatments, for example because of risks of long-term toxicity, logistical difficulties in attending for phototherapy and treatment-resistant psoriasis, there is a need for new therapies. Biologic therapies are a rapidly advancing area of therapeutics, which offer the opportunity to selectively target the inflammatory events that lead to the development of psoriasis.

Three TNF inhibitors are currently licensed for severe psoriasis (adalimumab, etanercept and infliximab) as well as the IL12/23p40 monoclonal antibody ustekinumab. In the UK these are approved for use in patients who have failed phototherapy and systemic therapy and who have severe disease as defined above. They have transformed the management of psoriasis for those with the most severe forms of the disease. Their long-term safety is now being carefully scrutinised; in the UK patients with psoriasis starting biologic treatment are enrolled in a five-year safety register (BADBIR) alongside a comparator group on systemic treatment, to determine their relative long-term safety. The complexities of managing severe psoriasis have led to the establishment of severe psoriasis clinics in specialist dermatology centres.

There is a strong pipeline of new therapeutics in late stage clinical development for psoriasis including, for example, biologic treatments that target IL-17 and small molecule inhibitors of Janus kinases.

TABLE 2 Profiles of phototherapy and systemic monotherapy in psoriasis (adapted from SIGN guideline 121)[3]

Therapy	Efficacy	Suitability in inducing remission	Suitability as maintenance treatment	Patient acceptability	Efficacy in psoriatic arthritis
Phototherapy	✓✓✓	✓✓✓		✓✓	
Methotrexate	✓✓	✓✓	✓✓	✓✓	✓✓
Ciclosporin	✓✓✓	✓✓✓	✓	✓✓✓	✓
Acitretin	✓	✓	✓✓	✓	
Fumaric acid esters	✓	✓✓	✓✓✓	✓	

HIGHLIGHTS

- Psoriasis may have an impact on an individual's quality of life similar to that of heart disease or cancer.
- Topical therapies should be offered first-line to most patients and choice of topical therapy will depend on the area involved and duration of therapy.
- Psoriatic arthritis is under-diagnosed and patients with psoriasis suspected of having psoriatic arthritis should be referred to rheumatology.
- Psoriasis is associated with an increased risk of cardiovascular disease and annual screening of those with severe disease to include BMI, diabetes mellitus, blood pressure and lipid profile should be offered.
- Biologic therapies that directly target the molecular steps in the development of psoriasis have transformed the management of severe disease.

FURTHER READING

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EDUCATION

SENIOR FELLOWS' CLUB PRIZE

The Senior Fellow's Club Prize for 2012 has been won by GE Walker and colleagues for their paper on 'Intravenous fluid use in the acutely unwell adult medical inpatient: improving practice through a clinical audit process'. This can be read in issue 3, 2012 at http://www.rcpe.ac.uk/journal/issue/journal_42_3/wood.pdf

A prize of £250 will be awarded to the first-named (or corresponding) author of an original research paper on a clinical topic, deemed by a panel of judges to be the best paper by a doctor-in-training (i.e. pre-consultant level) published in *The Journal of the Royal College of Physicians of Edinburgh* in 2013. The best paper will be selected by a panel of judges, including a senior Fellow, an active clinician and a member of the editorial team.

Further details may be obtained from the Editorial Office, RCPE, 9 Queen Street, Edinburgh, EH2 1JQ, tel +44 (0)131 247 3652 or email editorial@rcpe.ac.uk.

SELF-ASSESSMENT QUESTIONS

1. An 18-year-old woman has psoriasis mainly on her face. She is very embarrassed about it and missing lectures at university. It has not responded to moderate potency topical corticosteroid.
Which ONE of the following is the most suitable topical treatment option?

A. Tacrolimus.
B. Dithranol.
C. Calcipotriol.
D. Potent topical corticosteroid.
E. Tazarotene.

2. Which ONE of the following is NOT a recognised co-morbidity of psoriasis?

A. Depression.
B. Asthma.
C. Arthritis.
D. Diabetes.
E. Crohn's disease.

3. A 46-year-old man with severe psoriasis of six years duration has developed peripheral psoriatic arthritis over the past two years. Recent hand X-rays show erosions despite treatment with methotrexate 20 mg weekly for four months.
What is the most appropriate treatment?

A. Leflunomide.
B. Etanercept.
C. Prednisolone.
D. Sulfasalazine.
E. Acitretin.

4. A 45-year-old man has had psoriasis since his teenage years. This has been very extensive at times and was treated with ciclosporin, which was complicated by significant hypertension. He also received narrow-band UVB (NBUVB) phototherapy when younger. He has active psoriatic arthritis affecting the distal interphalangeal joints of both hands. His current severity scores are PASI 8.0, DLQI 12.
What is the most suitable next treatment?

A. Acitretin.
B. Adalimumab.
C. Psoralen and ultraviolet A (PUVA)
D. Methotrexate.
E. Ustekinumab.

5. A 22-year-old woman has many small (2 cm diameter) patches of psoriasis which have developed over the past two years. These are widely spread over trunk and limbs (BSA about 15%, DLQI 18). They have not responded to six weeks of treatment with a combination cream containing calcipotriol and a potent topical corticosteroid. She has no symptoms of psoriatic arthritis. She reports symptoms of depression.
What is the most appropriate treatment of her skin?

A. Methotrexate.
B. Etanercept.
C. Narrow-band UVB (NBUVB).
D. Psoralen and ultraviolet A (PUVA).
E. Topical dithranol.

This paper was originally published as part of the Dermatology module in the RCPE Online Continuing Medical Education Programme. Online CME, including the anwers to these questions, is available to Fellows and Members at: http://www.rcpe.ac.uk

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