PSORIASIS AND ITS MANAGEMENT

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SUMMARY

Psoriasis is a common, chronic erythro-squamous dermatosis affecting approximately 2% of the population and accounts for 10–20% of visits to a hospital dermatology unit. In this review article we discuss the epidemiology, pathophysiology and clinical features of psoriasis, and the pros and cons of the available therapeutic options.

Although psoriasis cannot be cured, a number of therapeutic interventions can induce clearance. Many patients have never been 'clear', generally as a result of under-treatment but the opportunity to be free from psoriasis (albeit temporarily) can dramatically improve quality of life. In the majority of instances it is possible to induce clearance of psoriasis, with the choice of treatment dependent on the individual patient's characteristics and expectations. Newer topical agents such as the vitamin D agonists are contrasted with older treatments such as dithranol and tar; phototherapy and photochemotherapy with ultraviolet B (UVB) and psoralen coupled with ultraviolet A (PUVA) respectively; and the three commonly used systemic agents, methotrexate, acitretin and cyclosporin. The limitations of the most commonly used topical treatments – when contrasted with phototherapy and systemic agents – are emphasised.

PSORIASIS, AN ANTIDOTE TO A DERMATOLOGIST'S EGO[1]*

Psoriasis is a chronic inflammatory dermatosis with a predilection for the extensor surfaces, scalp and nails, characterised by a fluctuating chronic clinical course.[2] As with most common dermatoses, and contrary to what is often stated, diagnosis is usually easily made, if not on the first visit then soon thereafter. The major clinical issues relate therefore not to diagnosis but to management and provision of appropriate care.

In this review after describing the clinical features and epidemiology of psoriasis, we wish to highlight areas of uncertainty where further work is required (rather than repeat what is already in the textbooks). In particular we adopt a critical approach to framing therapeutic questions.

Several points can be stated simply at the outset. First, it is almost always possible to clear an individual of psoriasis using either local or systemic treatment; the clinical issue is a matter of balancing risks and gains. Second, there appears to be an undercurrent of therapeutic nihilism, accentuated by a lack of provision of care, which means that effective remedies are underused. Many of the treatments available to the general practitioner (GP) or general physician are either without significant effect or of only moderate benefit. Effective treatment for the majority of patients will require hospital-based therapy within a dermatology department that places appropriate emphasis on patient outcomes rather than the number of new patients seen.

EPIDEMIOLOGY

Approximately 15% of patient contacts in general practice are for diseases of the skin.[3] Around 10% of these will be for the treatment or management of patients with psoriasis.[3] The prevalence of psoriasis, in the various northern European populations sampled is around 2% with, based on extrapolation of data from a variety of sources, an incidence of around 1–2/1,000 per year.[4,5] Data provided by ISD (Scotland) to the authors (personal communication) is in keeping with these incidence estimates.

Only one study[6] has looked at what proportion of individuals who are known to have psoriasis in primary care have been seen in hospital: the quoted figure is around 50%. There may be wide variation around this figure and further studies would be helpful. In the hospital dermatology department, patients with psoriasis account for around one-fifth of all attendances. This number reflects the large number of repeat visits patients make when attending for either phototherapy or for out-patient treatment with dithranol or tar.

The sex ratio of psoriasis is equal, and by age there would appear to be two peaks of psoriasis onset. The first is in late adolescence or early adult life, and the second in those aged 50 onwards.[7] The former group is more likely to have a family history of psoriasis and be HLA-Cw6 positive. These age-specific peaks refer to incidence rather than prevalence which, given the chronicity of the disorder, rises with advancing age although the detailed epidemiology is unknown. There are no known secular trends in incidence or prevalence.

The quoted population prevalence of psoriasis of ~2% seems to apply to most European populations but rates in Japan and China appear to be at least an order of magnitude lower. The reason for this is unknown but one possibility is differences in the prevalence of particular HLA haplotypes that may confer susceptibility to psoriasis.[4,5]

*Bechet 1934, quoted in Lomholt[1]

GENETICS

Psoriasis is genetically complex.[1, 8] A large number of twin studies have been published, including population-based studies from Scandinavia and Australia.[9, 10] Such studies report case-wise or proband-wise concordance amongst monozygotic twins of between 30% and 60%, and 10% to 25% for dyzygotic twins. Calculated heritability in some studies is around 80% and this still means that over two-thirds of monozygotic twins are not concordant. Based on a large number of Scandinavian families the lifetime risk of suffering from psoriasis if no parent, one parent or both parents have psoriasis is 0·04, 0·28 and 0·65 respectively. If there is already one affected child in the family, the corresponding risks are elevated to 0·24, 0·51 and 0·83.[11]

Genome-wide approaches have identified a number of loci predisposing to psoriasis. Almost one-half of the known variation attributed to 'genetic factors' can be 'explained' by markers within or close to the major histocompatibility complex (MHC). In keeping with this, it has been known for a long time that particular HLA groups, notably Cw6, show a strong association with psoriasis (odds ratios of ~10).[8]

ENVIRONMENTAL FACTORS

We are largely ignorant as to why patients develop psoriasis when they do, or of being able to explain the relapsing and remitting cause of the disease. The oldest recorded onset of psoriasis was in an individual aged over 100. Factors of relevance are as follows:

Infection and guttate psoriasis

Guttate psoriasis is characterised by the rapid onset of a large number of small lesions, with perhaps half of all cases being precipitated by streptococcal sore throats.[12] For many patients guttate psoriasis will be the first presentation of the disease, and it is more commonly seen in children and young adults. Beyond association with streptococcus, the role of other infections in precipitating psoriasis has not been studied. Human immunodeficiency virus (HIV) infection does not appear to increase the incidence of psoriasis but many patients report a marked worsening of their disease during the course of HIV/AIDS.[13]

Trauma

Psoriasis may appear at the sites of trauma, a characteristic known as the Koebner phenomenon. Psoriasis may thus appear at the sites of sunburn, or following surgery or biopsies, or even after simply scratching an area.

Drugs

Given the variable natural history of psoriasis, there is a tendency to ascribe changes in the course of the disease without good evidence. Some drugs are, however, accepted to precipitate or worsen pre-existing disease; these include lithium, antimalarials, beta-blockers and NSAIDs, although the evidence for the latter is poor and the magnitude of any risk uncertain.[14]

Alcohol and smoking

Some studies have suggested smoking or alcohol as a cause of psoriasis.[5, 15] The majority of such studies have been case-control studies, often based on a typical group of patients admitted to hospital. Nonetheless an alcohol-associated elevated risk still holds true even when studies are conducted on incident out-patient cases. The aetiological significance of these studies is difficult to assess. It is not clear how such associations operate, as we know very little about the descriptive epidemiology of psoriasis. Many dermatologists believe that there is an over-representation of high alcohol intake in a sub-group of patients with psoriasis; which way causality is pointing, however, is not clear, i.e. does the disease lead to increased alcohol consumption or vice versa?

One particular variant of psoriasis, palmoplantar pustulosis (Figure 1A), shows a high odds ratio with smoking (7).[16] Studies in which such individuals have subsequently stopped smoking suggest that the disease does not remit. By contrast, the odds ratios reported in other studies for plaque psoriasis are lower, centring around 2 to 3.[17]

Stress

Earlier accounts of psoriasis did not attribute any role to stress – however defined – in the disease. More recently, stress has been popularised as being implicated in precipitating or precipitating exacerbations of the disease as with many other diseases with a complex natural history.[5] Unfortunately the methodological rigour of most studies on this issue is poor, and robust experimentation based on a prospective study of individuals with clearly predefined definitions of life-events and stress is required.[18] Unfortunately, the view that stress is a significant factor in the natural history of psoriasis is widespread, particularly among patient groups.

PATHOPHYSIOLOGY

Psoriatic plaques are characterised clinically by erythema (due to an increase in blood flow and an increase in the dermal vasculature); and scaling and thickening (due to hyperkeratinisation of the stratum corneum, thickening of the entire epidermis, dermal oedema and inflammatory dermal infiltrate)(Figures 1B and 1C).[2,19] The clinical signs can therefore be explained by the inflammatory findings and epidermal hyperproliferation.[2, 19]

These features are reflected at the histological level where there is:

1. a greatly increased number of mitotic figures within the epidermis;
2. thickening of the epidermis but with relative thinning of the papillary tips;
3. the absence or diminution of the granular layer

and the presence of nucleated cells within the stratum corneum (parakeratosis), reflecting abnormal keratinocyte differentiation;
4. prominent vessel formation within the dermis; and
5. a marked inflammatory infiltrate of both polymorphonuclear leucocytes and lymphocytes but with characteristic acute neutrophil containing abscesses forming within the epidermis.

The original pathophysiological model of psoriasis, particularly following the success of methotrexate as a treatment, emphasised psoriasis as a primary disorder of epidermal hyperproliferation. The other abnormalities were considered secondary phenomena. History, or at least academic interest, then repeated itself when cyclosporin was noticed (by chance) to have a dramatic effect on psoriasis.[20] The success of this drug directed attention to the latent evidence on the role of the immune or inflammatory system, with consequently a renewed interest in the prominent CD4 dermal infiltrate and the idea that psoriasis is a T-cell mediated disease.[20] At present the exact relation between epidermal hyperproliferation and the inflammatory infiltrate remains unexplained although parallels can be drawn with other inflammatory processes, such as rheumatoid arthritis in which (synovial) hyperproliferation occurs in the presence of an inflammatory infiltrate.

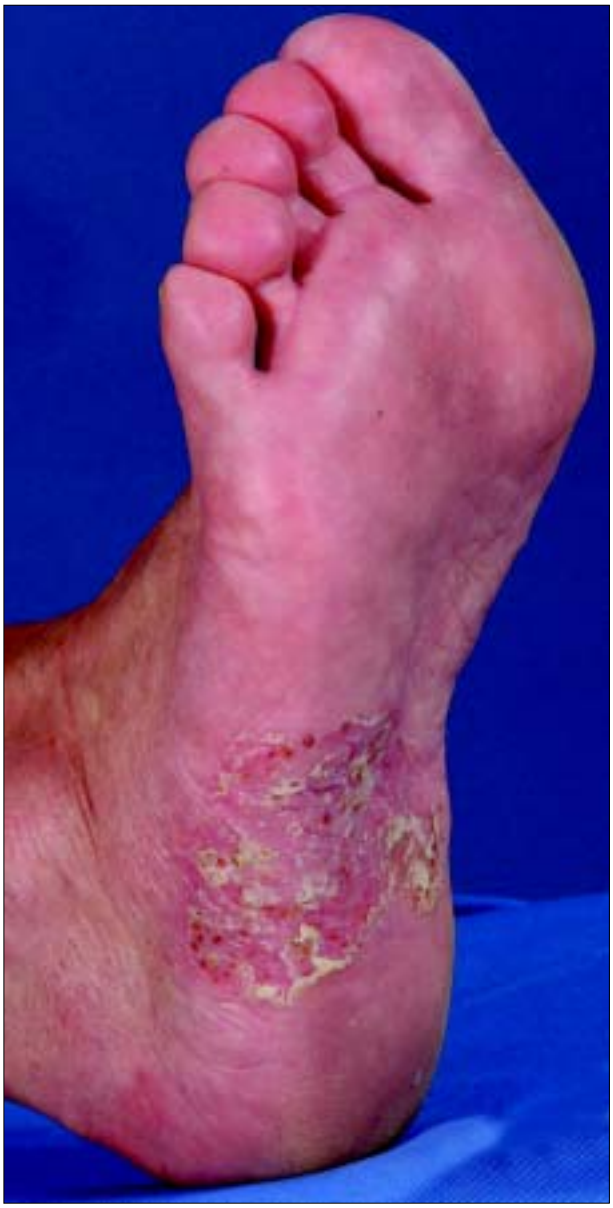

FIGURE 1A
Plantar pustulosis.

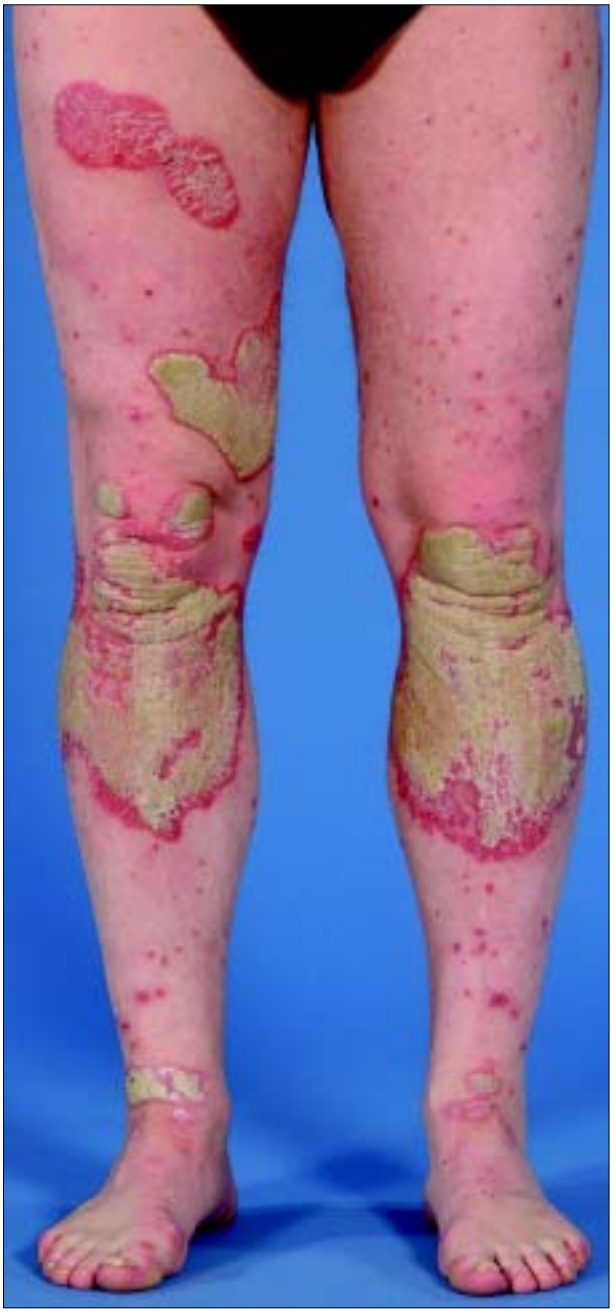

FIGURE 1B
Symmetrical hyperkeratotic plaques of psoriasis on legs.

CLINICAL TYPES OF PSORIASIS

The clinical pattern of psoriasis can be usefully classified

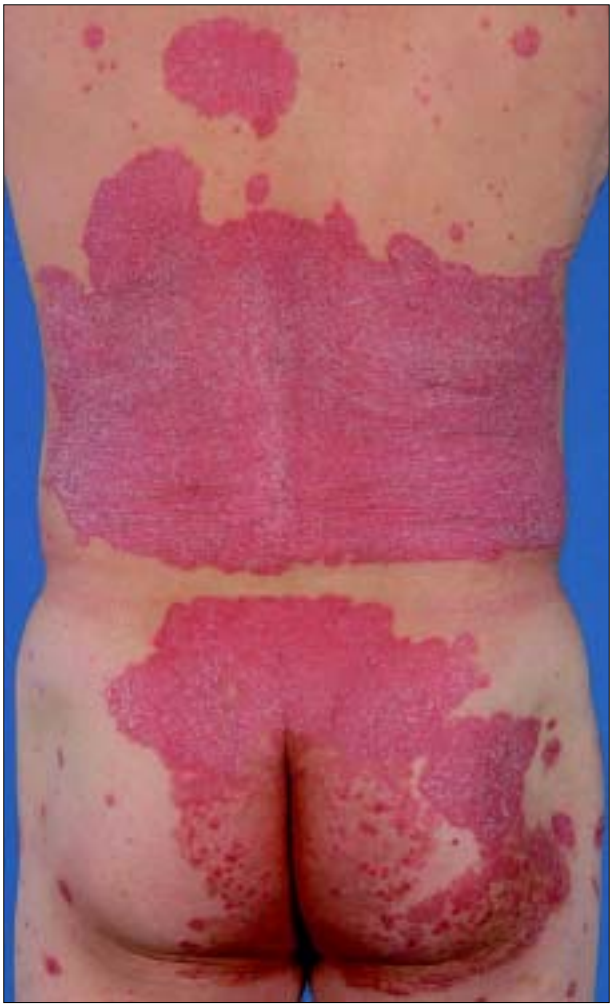

FIGURE 1C
Large confluent plaques of psoriasis on lower back and buttocks.

into a variety of types accepting that patients may move from one type to another, so that for instance a patient may present with acute guttate psoriasis in late teenage years, which then is followed by the onset of chronic plaque psoriasis, which may, on occasions, develop into acute episodes of generalised pustular psoriasis if the course of the disease is severe. Some people believe that palmo-plantar pustulosis (of the palms and soles) is a distinct disease.

Acute guttate psoriasis

This is characterised by a large number of small lesions often occuring in the aftermath of a streptococcal sore throat.

Chronic plaque psoriasis

This is characterised by fairly stable plaques of a variety of sizes but measuring greater than a centimetre across with a particular predilection for the extensor surfaces such as the elbows and knees.

Generalised pustular psoriasis

Characterised by anti-inflammatory changes in the psoriatic sites, the development of pustules in psoriasis may seem strange at a clinical level, but, when viewed in the light of the pathology and in the presence of microscopic microabscesses, it can be seen as an extreme of a continuum. Generalised pustular psoriasis can be a life-threatening condition with a variety of systemic consequences including hypothermia, high output cardiac failure and secondary sepsis. The patient may have thousands of small pustules forming large pustular sheets across much of the body surface.

Palmo-plantar pustulosis (pustular psoriasis of the palms and soles)

This is characterised by a pustular rash of the palms and soles. The pustules are sterile and may be viewed as representing one extreme of the microscopic polymorphnucleocyte abscesses seen in ordinary plaque psoriasis. Patients with this disorder may or may not have psoriasis on other parts of the body and may or may not have a family history of psoriasis.

Erythrodermic psoriasis

Psoriasis is one of the recognised and common causes of erythroderma. Such patients may present without the typical morphology of the psoriatic plaque but with a generalised erythema and oedema. In the absence of a clear history of previous psoriasis, a definite diagnosis may not be possible initially.

THERAPY

Choosing the right therapy for patients with psoriasis is often problematic (and frustrating) because of inadequate evidence over which course of action is superior; historical differences in treatment use (say between tar and dithranol); and lack of availability of facilities for in-patient therapy. Surveys suggest that patients believe their disease is under-treated and, as a broad generalisation, it seems that patients more readily accept the side-effects of the treatments than the physicians prescribing them.[21] An alternative way to express this is that physicians tend to underestimate the disutility patients feel. Undertreatment it often appears is camouflaged by routine underprovision of service.

The concept of clearance

Over the last quarter century a change in emphasis has occured on what constitutes the goal of treatments – to some degree this change has, in our opinion, been detrimental to patient care. When in-patient treatment with Ingram's dithranol regime was the norm,[22] the aim of therapy was to induce total clearance, or near-total clearance, and then wait until relapse occurred. In-patient admission is now no longer an option for the majority of patients because of the absence of in-patient facilities and, on a more positive footing, the development of efficacious out-patient treatments. Instead, many of the newer topical treatments widely used in primary care have no real ability to induce clearance of the disease;[23]

the patient is doomed to continue to use the agent on an indefinite basis or until natural history overtakes, or the patient gets fed up with the response and seeks referral to secondary care.

Alternatives to in-patient treatment do exist, and although they may be preferred by many patients, considerable uncertainties remain about their long-term risks compared with in-patient treatment. Given that clearance can nearly always be induced using ultraviolet therapy or systemic agents, a major management issue relates to how often such agents are used and how, often in the absence of detailed data, decisions can be made about risks vs benefits. In this situation the wide variation in 'clinical opinion' that exists is inevitable.

CLASSES OF THERAPY

Treatments for psoriasis can be usefully classed into four groups:

1. Topical agents requiring in-patient therapy such as dithranol or tar, which when used intensively have the ability to clear most or all of the plaques, e.g. Ingram's regime on in-patients.
2. Topical agents that are more 'patient-friendly' but less efficacious than those in class 1 and do not show a high rate of clearance, e.g. calcipotriol.
3. Ultraviolet radiation (UVB) or photochemothearpy (PUVA).
4. Systemic agents such as cyclosporin, methotrexate or retinoids.[24]

As a general rule most patients would start off with agents in class 2, and then move on to classes 1, 3 and 4 when they are seen in hospital. The reason for placing class 1 agents before class 2 is historical, but does provide a necessary perspective to understand the limitations in efficacy of class 2 agents.

Class 1 agents: Ingram and Goeckerman regimes

During the last century two intensive in-patient regimes were developed to treat patients with psoriasis as in-patients.[25] The Ingram regime is based around dithranol, while the Goeckerman regime is based around tar. Available evidence suggests that the Ingram regime is more efficacious but may require more skill on the part of nursing and medical staff. To achieve optimum results both these regimes require in-patient stays of three or more weeks, and considerable nursing and medical staff expertise. In the Ingram regime for instance, patients would have a tar bath, followed by exposure to a UVB source followed by application of dithranol in appropriate concentrations directly to the psoriatic plaques. These would then be covered with talcum powder and appropriate dressings, and the whole procedure repeated every 24 hours. Importantly the dose of dithranol would need to be chosen appropriately for different body sites and increased incrementally according to response and sensitivity. Such treatment would clear 80–90% of patients with a median of 21 days. The main hazards of the Ingram's regime are burning from the dithranol (or the ultraviolet radiation) and a brown skin staining that dithranol produces (that may take several weeks to resolve). Long term, such treatment appears remarkably safe, certainly in comparison with many of the treatments that are now more widely used.

The Goeckerman regime is based around high concentration tar and ultraviolet radiation, and usually requires in-patient admission. The main disadvantage of this regime is the pervading smell of tar.

In an attempt to make dithranol more acceptable as an out-patient-based therapy, short contact dithranol (SCD) was developed in the late 1970s and 80s.[25] The principle was that higher concentrations of dithranol could be used for a shorter period of time, and that there was a (beneficial) differential effect between the plaque and the normal perilesional skin in terms of dithranol absorption. In practice, when used as an in-patient treatment, SCD appears comparable but probably inferior to Ingram's regime for some patients but, in the out-patient setting, results are far worse than those obtained on in-patients.

Attempts have been made to use lower concentrations of tar and dithranol so that patients might be more inclined to use them at home. Despite claims to the contrary, however, it has not proved possible to dissociate efficacy from the concentration of the agents used, and the side-effects – in terms of irritancy or smell – are concentration-dependent. With dithranol preparations the lower the concentration, the higher the patient's acceptability, but also the lower the clinical effect. The same holds in general terms for tar; the more refined the tar is, the more socially acceptable it may be, but the lower the efficacy. When reviewing results of published systematic reviews and meta-analyses, it is important to remember that virtually all comparisons have been made between newer topical agents and dithranol or tar preparations used in a way that are not optimal in comparison with the original studies (such as the UK MRC trials).[26]

In summary, in-patient treatment with Ingram's regime is highly efficacious and safe. It requires considerable skill among nursing and medical staff, skill that is now possibly diminishing with the attrition of dermatological in-patients facilities. From a patient's perspective, if they can take the time for an in-patient treatment, this therapy is probably safer than anything else that has succeeded it, albeit more inconvenient.

Class 2 agents: topical agents that are more patient-acceptable but less efficacious than those in class 1

Emollients or keratolytics, such as salicylic acid, will reduce the amount of scale produced, which may be useful in

itself or may help in terms of application of other treatments such as ultraviolet radiation. The effects are, however, modest. Corticosteroids are widely used to treat psoriasis although in the UK their use is frequently frowned upon; in the US and in Europe they occupy a significant clinical niche. Their shortcoming is that although they can render plaques less visible, less indurated and less scaly, the plaques tend to reappear as soon as the steroids are stopped. Because of the known side-effects of steroids, principally, in this context, the induction of atrophy and striae, the duration of their safe use is limited. In the flexures, and some other sites such as the ears and hair margins, where application of dithranol or tar may be difficult, steroids are still widely used in the UK. In general, potent or very potent steroids such as betamethasone valerate or clobetasol proprionate are necessary.

A significant advance in the topical treatment of psoriasis was the development of vitamin D analogues,[27] which followed a clinical observation of improvement in psoriasis in a patient who had been treated with systemic vitamin D. Vitamin D has a multitude of actions in skin and its precise mode of action in this condition is unknown. Vitamin D preparations are now among the most widely used preparations for psoriasis in primary care. In general they are very well tolerated. They show a tendency to produce local irritation in some people and, if applied to large areas over too long a period, the possibility of causing hypercalcaemia should be considered. The effects of such preparations on psoriasis are a reduction in scaling and a reduction of the plaque thickness. They will rarely induce clearance at any significant rate above the expected from the disease's natural history, a major drawback to their use. Nonetheless because of the absence of suitable alternatives for a large number of patients they are widely used, especially in primary care.

Other topical treatments include vitamin A preparations, the role of which is at yet poorly defined, and various combinations of steroids with other topical agents.

Class 3 agents: phototherapy and photochemotherapy

Sunlight improves most patients' psoriasis. The advent of artificial ultraviolet sources with sufficient power at the beginning of the twentieth century led to their therapeutic use for psoriasis. Such ultraviolet treatment was combined with tar or dithranol as described above. It seems fair to say that throughout the majority of the last century such treatments were administered fairly uncritically and without much investigation of the appropriate wavelengths or dosage protocols that would exert the maximal clinical effect.

The great fillip to the use of phototherapy in dermatology was the advent of photochemotherapy by Fitzpatrick *et al.* in the early 1970s.[28] Prior to their work, sporadic papers described the effects of photosensitisers and ultraviolet A ('black light'), but Fitzpatrick *et al.* rationalised these studies and introduced oral (methoxy) psoralen as a photosensitiser coupled with ultraviolet A (P+UVA = PUVA). It is important to note that although commonly described as a 'light' or 'ultraviolet' treatment, photochemotherapy is, as the name implies, a combination of a drug and an ultraviolet ray. The ultraviolet ray is merely used to convert a pro-drug, methoxypsoralen, to the active drug locally.

There were two important consequences of the introduction of PUVA. The first was a highly efficacious out-patient treatment for psoriasis. The second was a renewal of interest in the study of ultraviolet and the skin, particularly in terms of the clinical usage of other types of ultraviolet such as UVB. In the following section we will describe the effects of photochemotherapy before moving on to the use of UVB.

Photochemotherapy – PUVA

The first randomised control studies reported by Fitzpatrick *et al.* showed that PUVA therapy had a dramatic effect on the clearance of psoriasis.[28] Subsequent studies performed in the UK showed that its effects were comparable with the then gold standard of Ingram's in-patient regime.[26] The advantage of PUVA was that the treatment could be performed as an out-patient with the patient attending between two and four times a week. Over the last quarter century such regimes of treatment have been rationalised and improved.

The exact mechanism of action of PUVA is unknown. The original rationale was based on the observation that PUVA inhibited epidermal hyperproliferation, then the formative model of psoriasis pathophysiology. However, PUVA also has a major effect on the inflammatory aspects of psoriasis and, experimentally at least, can be demonstrated to have effect on the function of the cutaneous immune system. Psoralen can be given orally, or applied topically, either in the form of a cream or added to a bath. In the UK, oral PUVA is the most common treatment modality. Methoxypsoralen is administered two hours before exposure to UVA; it is a pro-drug with little biological effect. Although it may induce nausea in some individuals it is widely distributed within the body. Psoralen intercalates within the DNA double helix but forms DNA crosslinks when subsequently exposed to ultraviolet at the appropriate wavelengths.

A highly efficacious treatment, PUVA produces clearance in >80% of patients, with 50% of patients being clear after a median of 17 treatments.[29] Short-term side-effects are nausea and burning. Erythema induced by PUVA has a different time course to that induced by UVB, with erythema peaking after three to four days.

The main limitation on the use of PUVA derives from long-term toxicity. Predictably, PUVA causes an increase in the incidence of non-melanoma skin cancer.[30] The risk depends on the cumulative dose of PUVA received and in individuals who have had over ten clearance courses of PUVA, the use of any further treatment needs to be carefully considered. The idea of using maintenance PUVA – continued once-weekly treatment to keep psoriasis in remission – has fallen out of favour largely because of concerns about safety.

Whether PUVA therapy causes a significant increase in melanoma incidence is as yet unclear, although most authorities believe it does.[31] The reasons for this are twofold. The first is that patients who have received a lot of PUVA develop PUVA lentigines (due to melanocyte proliferation), an indirect sign of effects of melanocyte growth control. The second is that follow-up studies from the US (but not Europe) suggest that there is an increased rate of melanoma in those who have received large amounts of PUVA.[31] Hopefully future work will provide more robust estimates of risk. Concern about melanoma is one factor that has led to increased use of UVB phototherapy in recent years.

UVB phototherapy

In most biological systems UVB has more biological potency than the longer wavelength UVA. Work by Parrish *et al.* in the 1970s showed that certain wavelengths of UVB, those over 300 nm, appeared more efficacious than others.[32] Prior to this work, and until the development of new lamps by Philips and other companies, most of the sources used for phototherapy emitted a significant component of ultraviolet C – shorter wavelength ultraviolet rays without useful clinical effects but with the capacity to induce burning – and also longer wavelengths of UV A which exerted little biological effect. Following this work, lamps were developed (by Philips) with a particular spectral output focusing around 311 nm (narrowband UVB).[33] It is widely believed that these lamps are more efficacious than broadband UVB regimes and they have come into widespread use in the UK and northern Europe (although within the US broadband lamps are still favoured).

Narrowband phototherapy is considered safer than PUVA, and although long-term follow-up studies in patients have not been conducted, this seems a reasonable assumption: consequently narrowband UVB is often now the treatment of choice for patients referred from primary care to a hospital. Clearance rates are lower in comparison with PUVA, however, and more treatments are required to induce clearance in 50% of patients (median of 25 for narrow band versus 17 for PUVA).[29] Remission times may also be shorter than with PUVA.[29]

The main hazards of UVB phototherapy are burning in the short term, induction of polymorphic light eruption in some patients and an increase in the risk of squamous malignancy of the skin. The magnitude of this risk is unknown but, based on extrapolations of tumour rates for patients with psoriasis overall, and prior experience of broadband sources, it would seem reasonable to argue that the risk may not be great and considerably lower than that seen for PUVA. Again, definitive studies are not available.

Class 4: systemic agents

A large number of systemic agents have been used to treat patients with psoriasis, with the three most widely used agents being methotrexate, acitretin and cyclosporin A.

Methotrexate

In early experimental studies of the use of methotrexate in patients with inflammatory arthritis, coexisting psoriasis was noted to improve. Following these observations methotrexate became widely used as a systemic treatment for patients with psoriasis, in particular as an agent to suppress disease activity in the long term.

Methotrexate is usually administered on a once-weekly basis with or without folic acid supplements. The original mechanism of action was thought to be inhibition of keratinocyte proliferation but subsequent studies cast considerable scepticism on this interpretation and it now seems likely that the drug is exerting its local effects via the immune system. Although methotrexate can be used to clear patients with psoriasis (acutely), its main clinical role is as an agent to reduce the burden of disease in patients who have required excessive clearance regimes using other modalities or who relapse quickly.

The main side-effects of treatment include nausea, bone marrow suppression, and in the long term, fibrosis of the liver and the lung. No randomised control trials are published on methotrexate use and it is the general clinical opinion that it does not work in all patients but is effective in more than half the patients it is prescribed for. The dose needs to be titrated against response and 25 mgs a week may be required. Strict monitoring of blood and liver at three-monthly intervals, once the effective dose is established, is required. Most argue that the hepatic side-effects, including the development of hepatic fibrosis, are greatest in the presence of other liver diseases or hepatotoxins: patients are therefore advised not to drink alcohol.

Monitoring of hepatic status has proved problematic and a number of solutions have been proposed over the years, none of which have come into routine clinical practice. Originally annual liver biopsies or biopsies after the administration of every 1·5 g of methotrexate (cumulative dose) were proposed. There now appears to be less enthusiasm for biopsies and many physicians would start patients on methotrexate and, if there were useful effects

which were tolerated, only then carry out a biopsy and take advice from local hepatologists.[34]

Acitretin

Acitretin is an aromatic retinoid, widely used in the treatment of psoriasis, the clinical place of which is still, however, poorly defined. Retinoids have a multiplicity of actions in skin and, at least based on basic biology, their therapeutic actions in psoriasis still remain a mystery. There are large international differences with regard to their use; in some European countries, for instance, the addition of retinoids is almost routine to PUVA treatment (at least in men), whereas in the UK their use is more restricted. Available trial evidence on the use of retinoids in psoriasis is too poor to base clinical practice on. European studies were non-randomised whereas the UK studies were smaller. The authors' view is that retinoids seem to have a very definite effect in some individuals but that it is difficult to know which patients will benefit. Side-effects include dry lips and drying of the other mucosa, hair loss and most worrying of all, retinoids are known to be potent teratogens. Acitretin metabolism is such that patients are advised not to conceive for at least two years following cessation of the treatment. Many centres combine retinoid use with PUVA therapy, justifying the combination on the grounds that a lower dosage of PUVA is required. This may be true, but there is little evidence to believe that this translates into a diminution in the relevant biological end-points for cancer.

Cyclosporin A

Cyclosporin A, in a pattern of clinical discovery now the norm, was shown to have a beneficial effect on psoriasis when it was administered as an immunosupressant in organ transplant recipients who had coexisting psoriasis.[35] The drug is arguably the most effective systemic agent, certainly when used over the short term, and has become widely used as an alternative to clearance with photochemotherapy or in-patient stay in many patients.[35] Cyclosporin is administered at a dose of 2·5–5 mg/kg, although lower doses may be efficacious, and is usually prescribed over a six to eight-week-period with an expectation that ~ 80% of patients will clear or substantially improve. The hazards of cyclosporin use are well known and include hypertension and deterioration in renal function and in the long term – based on extrapolation to its use in other conditions – an increased risk of neoplasia of cervix and skin and lymphoma, although the magnitude of these risks is unknown.

CONCLUSIONS AND FUTURE ISSUES

Psoriasis remains a common and incurable inflammatory skin disease that accounts for a large amount of a dermatology centre's workload. In general, most patients will require – if optimum treatment is to be instituted – treatment at a specialised psoriasis centre, which in the UK usually means hospital-based treatment. Despite the fact that this disease is incurable, there have been major advances in the therapy of psoriasis over the last 25–30 years: photochemotherapy, the rationalisation of UVB phototherapy and systemic immunosupressives and retinoids. Nonetheless there are major issues remaining surrounding the provision of care, and our ignorance of the natural history of psoriasis without, and with, therapeutic intervention.

When a patient presents with guttate psoriasis in their late teenage years we cannot provide any useful figures in terms of what will happen to them, i.e. whether they are likely to develop bad psoriasis or not. Similarly we are ignorant of the factors that determine the pattern of relapse and remission. Such issues are important because in patients who are going to suffer infrequent relapses occasional clearance courses of cyclosporin or PUVA may be appropriate. By contrast, in those who relapse quickly, long-term therapy with methotrexate or acitretin may be more appropriate because the cumulative toxicity of multiple courses of PUVA may be considerable.

Other issues relate to the limitations of randomised control studies in guiding clinical practice. Although outcomes for a disease such as psoriasis often can be measured over the short term, the main limitation for some therapies is long-term toxicity. When patients frequently swap from one treatment to another it is very difficult to dissociate the individual toxicity of the various agents used. For instance, many patients with PUVA will, at various times, have been treated with cyclosporin and methotrexate. Long-term randomised control trials are not feasible if for no other reason than patients will not consent to take part in such long-term studies. The corollary, however, is that our risk estimates for many of the treatment side-effects are both biased and imprecise.

Finally, as mentioned elsewhere, a major issue in the UK, is the systematic under-provision of specialised care. It is still almost routine for patients to be referred with psoriasis which has in practice been treated inappropriately for over a 20-year-period, with scant regard to what we do know about the results of therapeutic intervention, and for the same patients to be amazed at the relative safety and efficacy of treatments such as narrowband phototherapy. This under-provision of care in Scotland compared with most Western European countries is unlikely to continue indefinitely. The advent of the newer biologicals,[36, 37] many of which show efficacy for psoriasis although their clinical place remains unclear, will only serve to exacerbate the gap between limited access to care and what can be achieved therapeutically.

The management of psoriasis has been transformed over the last 25 years, changing what was once a disease that was only amenable to therapy with systemic drugs or intensive in-patient care: phototherapy has revolutionised

the management of psoriatic disease for many people. Current research is focused on a number of different avenues.[36,37] A number of novel immunomodulatory drugs are currently under clinical development. These take advantage of two main therapeutic strategies. First, T-cell targeted approaches such as the fusion protein Alefacept and humanised monoclonal antibody Eflalizumab; and second, cytokine targeted therapies including TNF alpha-blockers such as Infliximab and Etanercept.

At the same time attention remains focused on how current therapies could be used more effectively and safely.[38,39] For instance, modern protocols of UVB may compare well with PUVA, and with considerable less toxicity. Similarly, combination therapy between topical treatments and phototherapy may prove worthy. As for many skin diseases, the major pace of advance is after the therapeutic agents have been introduced to the clinic.

KEY POINTS

- Psoriasis is a chronic erythro-squamous dermatosis affecting 2% of the population.
- Polygenetic and environmental factors play a role in its aetiology.
- Pathophysiological mechanisms include:
  - epidermal hyperproliferation;
  - vascular proliferation; and
  - inflammation.
- Choice of treatment depends on individual patient characteristics.
- Treatment options include:
  - topical;
  - phototherapy: UVB, PUVA; and
  - systemic agents.
- Immunomodulatory therapies are a promising new development.

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