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Management of severe adult atopic dermatitis

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In common with many units, we run a specialist atopic eczema clinic that receives both secondary and tertiary referrals. Investigation into possible provoking factors includes RAST testing and patch testing where appropriate. The mainstay of treatment for moderate to severe atopic eczema remains topical steroids and emollients. Our specialist nurses play a key role in education and in particular demonstrating topical treatments – including bandaging. It is surprising that many patients have not previously been shown how to apply the treatments prescribed. Nevertheless, despite optimizing topical treatment protocols, a proportion of patients require hospital admission or second-line therapy. Our recent double-blind, randomized, controlled trial of narrow-band UVII vs. UVA (as used in PUVA) vs. placebo has confirmed that narrow-band WB phototherapy is an effective adjunctive treatment in moderate to severe atopic eczema. This trial also highlighted the value of recording disease activity (e.g. SASSAD) in individual patients following a change of therapy. UVA1 may be useful for acute severe atopic eczema but this UV source is only available in limited centres within the UK. Selected resistant patients or patients with acute flares are considered for short-term cyclosporin therapy. Azathioprine is widely used by consultant dermatologists in the UK as a second-line agent – despite the lack of evidence of efficacy. We are currently conducting a randomized placebo-controlled trial to address this issue. The importance of checking thiopurine methyl transferase (TPMT) prior to initiating azathioprine therapy has been emphasized. Our pilot data, with a dosage regime based on the TPMT result, suggest that patients may achieve a longer-term remission after a relatively short course. Mycophenolate mofetil has been reported to be effective in an open trial and methotrexate is also used but there is a lack of published evidence. The advent of topical tacrolimus and ascomycins, which have been shown to be effective in controlled trials, appear to be a promising development in the management of patients with moderate to severe atopic eczema and may lead to reduction in the use of systemic agents.

Retinoid refractory acne vulgaris

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Most patients respond to oral isotretinoin very well, when it is prescribed appropriately. However, there are some patients who remain refractory to treatment. This presentation will discuss the several reasons for this refractory state. Very uncommonly a mistaken diagnosis such as epidermoid cyst or steatocystoma multiplex may be responsible. Although most patients respond well to a dose of 0.5–1.0 mg/kg for 4–8 months, a small number of patients need either a higher dose or a longer duration of therapy. Very often there is no obvious explanation for this, except that in a small number of patients there may be drug inter-reactions that somehow interfere with the absorption and metabolism of isotretinoin. Recently we had two patients who had previously responded to oral isotretinoin but who failed to show an improvement in their acne. The mechanism for this is not known. Certain types of acne, especially in those patients with many whiteheads, and in particular many macrocomedones, may also be refractory to treatment or flare badly whilst on roaccutane treatment. Such patients need gentle cautery of the large comedones. Other explanations include patients with significant endocrine disease such as polycystic ovarian syndrome or late onset congenital adrenal hyperplasia. The development of significant side-effects, be this mucocutaneous, systemic or laboratory events are other explanations for a refractory state, simply because the patient is not able to take the appropriate dose of the drug. Some patients develop significant increased inflammation whilst on oral isotretinoin necessitating the use of oral, topical or intra-lesional steroids.

Management of palmoplantar pustulosis

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Palmoplantar pustulosis or chronic palmoplantar pustular psoriasis (PPP) is an uncommon but disabling and recalcitrant pustular dermatosis affecting the palms and soles. Its onset is strongly linked to cigarette smoking and once it is established it tends to progress gradually over years or decades. Its relationship to psoriasis is disputed. Treatment is unsatisfactory and many different therapeutic manoeuvres have been advocated. We have performed a Cochrane systematic review of PPP in order to assess the evidence for efficacy of treatments for PPP. Randomized controlled trials (RCTs) of interventions for PPP were sought by interrogating the Cochrane Controlled Trials Register, Medline and Embase for the terms (PALM* or PLANT* or SOLE* or BACTERID) and (PUSTUL* or PSORIA*).

Additional searches were undertaken by cross-checking with two databases of psoriasis trials collated in our department and by the European Epidermo-Epidemiology Network (EDEN). We found 23 RCTs that met our inclusion criteria. These comprised eight trials of systemic retinoid monotherapy [six vs. placebo, one vs. psoralen photochemotherapy (PUVA), one comparing two retinoids]; four trials of PUVA or retinoid-PUVA (two PUVA vs. placebo, two PUVA vs. PUVA plus systemic retinoid); two trials each in which cyclosporin, hydroxyurea, a tetracycline or colchicine was compared with placebo; one trial of Grenz ray therapy vs. placebo; and two trials of topical corticosteroids under hydrocolloid gel occlusion compared either with steroid alone or with additional PUVA therapy. Many of the studies were of short duration with small numbers of participants. Outcome measures used varied considerably between studies. The following interventions were shown to be significantly better than placebo in reducing disease severity scores in PPP: etretinate, liarazole, PUVA using oral psoralen, low dose cyclosporin, Grenz ray therapy, tetracycline antibiotics. Acitretin was of equal efficacy to etretinate. Overall however, few patients achieved good or excellent results. Potent topical corticosteroids were shown to be more effective if used under occlusion. The addition of PUVA to such therapy was of no extra benefit. No RCT of methotrexate therapy was found but evidence from one open study suggests that it is of limited efficacy. The following interventions were also of no or minimal benefit: PUVA using topical psoralen, hydroxyurea, colchicine. The best results were achieved with systemic retinoid therapy both on its own (40% good or excellent response) and in conjunction with oral PUVA (68% clearance) when it was more effective than topical or oral PUVA alone. The value of systemic retinoids for long-term therapy is, however, diminished by their side-effects. The ideal therapy for PPP remains elusive.

Management of refractory plaque psoriasis

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The treatment of limited extent plaque psoriasis in the majority of cases is a routine procedure for dermatologists and only a small number of patients need a change of the chosen regimen. However, in patients with widespread plaque psoriasis treatment can be hampered for various reasons; in particular, the use of a systemic regimen or UV light and all their combination modalities may be restricted by individual factors such as concomitant diseases, personal risk factors and previous treatments. In another group of psoriasis patients with high disease activity and frequent relapses after each treatment course effective intervention can be difficult. In mild forms of plaque psoriasis a combination of different topical agents, mainly with sequential use, are given. For several of these combinations like such as D3 and its analogues, and topical corticosteroids clinical studies have shown synergistic mechanisms. A next step of treatment is the introduction of occlusive treatment. In moderate plaque psoriasis topical agents are usually combined with W-light (LTVB or PUVA). Salt-water bathing plus UVB is an alternative modality. For severe forms of plaque psoriasis systemic compounds are combined with topical agents. The systemic retinoid acitretin may also be combined with PLIVA. In very severe cases the combination of systemic compounds such as cyclosporin and methotrexate may be adequate. Initial treatment with new biological compounds such as monoclonal antibodies targeting multifunctional cytokines such as tumour necrosis factor α, or which interfere with T-cell activation (interleukin-2 receptor antibodies) seems to be highly effective in active or triggered severe plaque psoriasis. A better definition of the type of psoriasis in the individual patient, as well as the recognition of risk and trigger factors, will help in choosing 'tailored' therapy. Records of previous treatment results further help to define an individual pattern of plaque psoriasis which may enable the dermatologist to predict treatment outcome with a good reliability. Combination of different regimens, rotation between them and sequential use of systemic registered compounds may help to prevent refractory diseases states. The limited use of new biological compounds may further help to treat patients with a history of unresponsive plaque psoriasis.

Management of scleroderma

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Systemic sclerosis is characterized by excessive deposition of extracellular matrix components into various internal organs and the skin. This is due to the development of fibrosis following an initial Raynaud's phenomenon and an inflammatory reaction. Although some of the basic principles in the pathophysiology of the disease are partly understood, we still lack a detailed knowledge of the initial processes. Therefore, therapy of systemic scleroderma is symptomatic and needs to be closely adapted to the subsets of the disease and to the specific involvement of affected organs. This includes the treatment of vascular lesions and the inflammatory reactions, whereas management of the fibrotic processes is still very limited and restricted to experimental protocols. Early detection of kidney and cardiac involvement is required, and the early diagnosis of pulmonary hypertension has a critical impact on the life expectancy of the individual patient. Although no causative treatment of the disease is available, organ-specific management of complications together with general symptomatic treatment modalities and detailed counselling of the patient are of tremendous help and can considerably in modifying the development of the disease.

Pityriasis rubra pilaris some reflections

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Some reflections. I have presented a working classification of five types of PRP which gives a guide to prognosis and helps to

consider like-with-like for research purposes. To focus unduly on taxonomy only obscures the more important aspect of aetiology. After many years of looking at PRP there remain many outstanding problems. It is clear that classical adult PRP has little to do with the other types aetiologically. The clinical features were reviewed and are not repeated here as they can be found in the standard texts. I have focused here on problems that may provide clues for others to advance the study of PRP.

Psoriasis or PRP? There is an enigmatic relationship with psoriasis which is difficult to penetrate:

- relative resistance to drugs usually effective in psoriasis, such as topical and systemic steroids, methotrexate, cyclosporin;
- normal numbers and distribution of peripheral T-cell markers;
- absence of prominent even parakeratosis despite an enhanced epidermal turnover;
- sparse inflammatory infiltrate lacking intra-epidermal neutrophil migration;
- absence of a PRI? arthropathy;
- personal family history of psoriasis in PRI? patients lying half-way between that of the general population and of psoriasis patients;
- a patient with clinically and histologically unequivocal PRI? cleared in 3 years except for occipital pityriasiform scaling. Ten years later plaques of clinically and histologically unequivocal psoriasis developed -coincidence of two diseases or PRI? becoming psoriasis?

Further observations. A few patients have repeated attacks of PRP separated by intervals of several years. The morphology in each episode is that of classical PRP, not PRP on one occasion and psoriasis on another. The erythema in PRP shows with a striking orange hue not limited to the palmoplantar keratoderma, so not simply reflecting the thickness of the callus of the keratoderma (red + yellow = orange). Carotenoids and retinoids are yellow or red but their levels in PRP are normal. Could there be some significance that hypovitaminosis-A induces localized follicular hyperkeratosis with histopathology similar to that of PRP?

Pathogenesis. What is the mechanism of production of the rash? The initial lesion is an erythernatous macule soon followed by areas of perifollicular erythema, which only later produce a hyperkeratinized follicular plug. The erythema triggers the localized burst of epidermopoiesis showing first as a follicular plug as the follicle is a column of epithelium. At this stage the inter-follicular epithelium shows hyperkeratosis only visible histologically as it does not possess the vertical 'epidermal escalator' of the follicle. In time the inter-follicular epidermis 'catches up' with the hyperkeratosis seen at the follicular orifices. This is exactly what is observed clinically as follicular papules coalesce into two's, three's then many lesions, producing confluent erythema. This process typically spreads in a cephalocaudal direction. Epidermal turnover is some six- to 10-fold more rapid on the head and neck than the legs. An increase of 10% in the stimulus to epidermopoiesis (as found experimentally) if sustained, will in time produce the observed evolution of PRP – early confluent erythema on the head and neck, palms and soles (fast turnover), follicular papules on the trunk becoming confluent, involvement of the legs last. If this supposition is correct the problem can be stated thus:

What is the abnormal stimulus to vasodilation showing first at the follicles and from which the clinical features develop? A number of patients have repeated attacks of PRP separated by intervals of several years. In each case the morphology is that of classical PRP, not PRP on one occasion and psoriasis on another.

PRP shows an erythema with a striking orange hue visible not only on the palmoplantar keratoderma – so not simply a function of the thick callous of the keratoderma – but all over the body (red + yellow = orange), carotenoids and retinoids are yellow or red but their levels in PRP are normal. Is there some significance that hypovitaminosis-A induces localized follicular hyperkeratosis with histopathology similar to that of PRP? The relative rarity of PRP make it a difficult disease to study but it is hoped that these reflections based on personal experience of many cases may provide some clues to a challenging condition.

Further reading

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Cutaneous lupus erythematoses

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The clinical features of the major types of cutaneous lupus are well known. The three broad categories of discoid lupus, subcutaneous lupus and acute cutaneous lupus describe particular entities with generally discreet clinical features. However there is considerable overlap between these forms and the initial focus of management of patients presenting with cutaneous signs of lupus erythematosus consists of establishing the degree of systemic involvement present. In those patients with systemic disease the over-riding therapeutic need is for control of the systemic features of the condition. Cutaneous disease will normally respond at the same time. However there are many patients who have cutaneous disease as their major

disease presentation. In these, choice of therapeutic option depends on the extent of cutaneous involvement, the time course of disease and the presence or absence of scarring. Whilst there is general agreement that first-line therapy with sunscreen, topical steroids and then if necessary anti-malarials is effective in the majority of patients (around two-thirds), subsequent therapy is based more on anecdote and experience than hard evidence. Being female, smoking and having extensive disease are features that often go together and lead to relative resistance to therapy. Once a single anti-malarial has failed in treatment, combination anti-malarials, dapsone, oral gold, methotrexate, thalidomide and many other agents have all been used though clinical evidence in support of their use is noticeable by its absence. Short courses of oral steroids are also often necessary in patients with severe and extensive disease as well as those with scarring. This talk will review the spectrum of disease, and the available treatment options.

Management of the nails in inflammatory dermatoses

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All clinicians will be familiar with the typical protective measures that can be combined with topical steroid treatments in inflammatory skin diseases affecting the nail. However, there are choices concerning the strength of the treatments, how they might be applied and for how long. In addition there are topical alternatives to steroids in some instances, such as calcipotriol and the oral nonsteroidal anti-inflammatory nimeluside, in hyperkeratotic pustular variants of psoriasis.

In this presentation we will also cover the further alternative of injected steroid, detailing the technique, selection of the subject and pattern of injection according to different practitioners. This is of relevance mainly in nail psoriasis, but can also be helpful in hyperkeratotic eczema, lupus erythematosus and some manifestations of lichen planus.

Nail lichen planus represents a particularly resistant category of nail disease and justification of potent systemic therapy may require nail biopsy to provide diagnostic certainty. Unlike in psoriasis, potent therapy may be justified in children as well as in adults and may take the form of local or systemic injected steroid as well as courses of oral steroids lasting for several months. In children there is a spectrum of nail disease where the rough nails of '20 nail dystrophy' may be in the nondestructive category of a histologically eczematous process, or may be lichen planus. The latter is at risk of progression with scarring, especially in children of Asian origin.

In addition to steroid in its various forms, there are other treatments for psoriasis and lichen planus that cover a range of mechanisms. These include 5-fluorouracil, dithranol, cyclosporin, methorexate and oral retinoids as well as forms of electromagnetic radiation such as PUVA16 and superficial X-ray. As a final resort, certain forms of dystrophy wholly resistant to medical therapy may necessitate nail avulsion and matrix ablation. This is mainly seen with upgrowing big toenails and pincer nail deformity.

Dermatomyositis

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Dermatomyositis (DM) is one of the idiopathic inflammatory myopathies. A set of criteria to aid in the diagnosis and classification of DM and polymyositis were first proposed in 1975 by Bohan and Peter. Four of the five criteria are related to the muscle disease: progressive proximal symmetrical weakness; elevated muscles enzymes; an abnormal electromyogram; and an abnormal muscle biopsy; while the fifth was the presence of compatible cutaneous disease. Subsequently it has been recognized that there are many patients with compatible cutaneous disease that do not have initial manifestations of their muscles as defined by clinical weakness and elevated enzymes. Some of these patients have subtle changes on biopsy, electromyogram or MRI at diagnosis, and some develop these changes and possibly clinical manifestations later, while a small group of patients never seem to develop clinical muscle disease.

In the patient with amyopathic DM the prognosis is good in the absence of malignancy. For patients with muscle disease, the prognosis depends upon the severity of the muscle disease, the presence of lung disease, oesophageal dysfunction and/or malignancy. Children and adolescents with DM often develop calcinosis that can result in disability or discomfort.

Classically, the diagnosis of DM is confirmed by the presence of typical muscle symptoms and findings along with elevated muscle enzymes, or an abnormal electromyogram and/or an abnormal muscle biopsy. Recently MRI became widely available and abnormalities of this test might be useful in diagnosis.

Treatment provides control of the muscle inflammation and results in a return to normal function of the patient who might otherwise become disabled from the weakness. The skin disease is often symptomatic and is cosmetically displeasing, therefore the goal of therapy is to relieve the symptoms and improve the patient's self-image and ability to interact with other people. Some patients with DM have an associated malignancy, and treatment of the malignancy might in some patients result in a control of the disease process. In children with DM treatments are aimed also at the prevention of calcinosis, or when the calcinosis occurs, at its eradication.

This presentation will focus on two issues: the relationship of DM to internal malignancy, including an approach to the search for cancer and the management of the patient with DM.

Differentiation, investigation and management of oral ulceration

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There are over 40 clinically distinguishable types of oral ulceration. These range from the common types of recurrent aphthous stomatitis (RAS) to very rare conditions such as histiocytosis. The severity of ulceration also varies from localized traumatic ulcers to primary or secondary carcino-

mas. It is therefore more important to know when to treat, when to refer and what to ignore than it is to diagnose every lesion. Oral ulceration can be divided into four main clinical groups: recurrent ulceration, persistent ulceration, single episodes of ulcers, and single persistent ulcers. RAS affects up to 10% of the adult population. There is good evidence of cytotoxicity to oral epithelial cells as a causative factor.

Recurrent oral ulceration includes the three main types of RAS, but also Behçet's syndrome and recurrent erythema multiforme. Persistent ulceration includes:

- dermatological conditions such as pemphigoid, pemphigus and ulcerative lichen planus;
- gastrointestinal conditions such as Crohn's disease and ulcerative colitis; and
- haematological abnormalities including haematinic deficiencies and anaemias.

Most single episodes of ulcers are due to infections whilst single persistent ulcers should be regarded as malignant until proved otherwise.

Disease severity scores are now available which take into account the extent and severity of conditions before and after therapy. Haematological deficiencies can contribute to the severity of symptoms in most forms of oral ulceration. In mucous membrane pemphigoid (MMP), three clinical forms are recognized and indirect immunofluorescence can be useful in monitoring disease progression. Oral pemphigus vulgaris is associated with desmoglein 3 autoantibodies and titres can be usefully monitored. Systemic steroids, azathloprine and colchicine remain useful therapies in the more severe forms of oral ulceration.

Management of hidradenitis suppurativa

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Hidradenitis suppurativa (HS) is a skin disease that affects predominately apocrine gland-bearing skin. The absence of a confirmatory test or specific features can make an early diagnosis difficult. It is characterized by deep abscesses, which are recurrent, sinus tract formation and scarring in more advanced disease. Disease activity is usually remarkably symmetrical with axillae and ano-genital regions affected most often. Other sites, breasts, nape of neck and waistband, become involved as the condition progresses. Sinus tract formation has been designated the hallmark feature. Early pathology shows follicular occlusion, not apocrinitis, and therefore HS is best considered an inflammatory disease originating from the hair follicle. Current treatment is derived mainly from empirical attempts to control the disease. Anti-acne antibiotics such as tetracyclines or macrolides are recommended. Only topical clindamycin has been shown to have an effect in a randomized controlled trial (RCT). More severe disease may demand oral clindamycin. If specific pathogens such as anaerobes are isolated then an appropriate antibiotic can be selected. Hormonal therapy with cyproterone acetate and ethinyloestradiol proved effective in one RCT but doses were high and continued use raises safety concerns. Steroid therapy has its advocates but a common experience is an initial response followed by relapse. Intra-lesional steroids can be useful for localized disease. Other immunosuppressive agents such as cyclosporin have been reported to be of help. Retinoids would be expected to be helpful based on the relationship between HS and acne but isotretinoin appears unhelpful; acitretin seems better. Success with surgery is proportional to the radicality of surgery. Incision and drainage carries a recurrence rate of 100% while radical excision has a recurrence rate of 25% at a median interval of 20 months. Careful laying open of sinus tracks is seen by many as the best compromise.

Management of severe acne rosacea

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Rosacea is a common facial disease. Clinical manifestations range from mild to severe, including several strange forms. These include: ophthalmo rosacca (ocular rosacea); conglobate rosacea; Gram-negative rosacea; rosacea fulminans, and rosacea fulminans in pregnancy. Treatment is either topical for mild or systemic for severe rosacea. Systemic drugs include tetracycline, isotretinoin, metronidazole, and glucocorticosteroids. The management of severe rosacea will be discussed with typical case presentations.

Systemic immunosuppressant therapy in childhood

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The indications for systemic immunosuppressant therapy are much the same in children as in adults. Perhaps the most important difference is the need in a child to consider more carefully the patient's likely future therapy requirements. This need reflects a justifiable anxiety concerning the longer-term toxicity associated with some of these drugs. It is obvious that special attention should be paid to the dosage regimens that are appropriate in children. However, otherwise the principles of treatment are essentially the same as in adults.

This talk will focus on the use of azathioprine in atopic eczema, methotrexate in psoriasis and linear morphoea, and intravenous methylprednisolone in severe muco-cutancous erythema multiforme and toxic epidermal necrolysis.

The value of azathioprine as a treatment for severe childhood eczema was greatly increased by the elucidation of the metabolic pathways for this drug, and by the development of an assay for thiopurine methyl transferase to allow detection of those at greatest risk of myelosuppression. We now treat children with normal TPMT levels with 3 mg/kg per day with gratifying therapeutic response and limited requirement for monitoring of blood counts and liver function. More recently we have successfully treated TPMTHL heterozygotes with doses of

around 1.5 mg/kg per day. We now consider azathioprine as superior to cyclosporin as a systemic therapy for atopic eczema.

The value of methotrexate in adults with plaque psoriasis and generalized pustular psoriasis is well established. It is equally useful in children with these disorders, and the most appropriate dosage appears to be in the region of 0.3–0.4 mg/kg as a single weekly dose. Children generally tolerate oral therapy well. Methotrexate also appears helpful in arresting the progression of linear morphoea, both in the case of coup de sabre lesions and progressive hemi-facial atrophy, and in limb lesions that are interfering with joint mobility or are causing profound lipoatrophy.

Intravenous methylprednisolone appears to be of value in several acute dermatoses in childhood, but is most commonly used at Great Ormond Street Hospital in the hope of arresting progression of severe muco-cutaneous erythema multiforme and toxic epidermal necrolysis. Various dose regimens are used in children, but in our unit we use a dose of 20–30 mg/kg per day, up to a maximum of 500 mg, for 3 successive days. Each dose is given over period of 2 h with frequent monitoring of vital signs, particularly blood pressure.

Management of urticaria

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Urticaria is predominantly due to release of mast cell mediators, mainly histamine. Chronic idiopathic urticaria, in which disease activity continues on most days for more than 6 weeks and there is no evidence of a physical urticaria or urticarial vasculitis, is common. An external cause is rarely identified even if a thorough history and appropriate investigation based on this are undertaken. However, approximately 50% of patients with chronic idiopathic urticaria (CIU) have a serum histamine releasing factor present. In one-third of patients with CIU this is an IgG autoantibody directed against the high affinity IgE receptor (FceRI) or less frequently against IgE. Patients with autoinimune urticaria, are clinically more severe. Urticaria can affect the quality of life markedly, being comparable to that of patients awaiting triple coronary by-pass surgery.

The rational management of urticaria takes account of likely causes and mediators involved. However explanation and attention to general measures such as minimizing stress, overheating and alcohol are important. Aspirin, nonsteroidal anti-inflammatory drugs and opiates should be avoided if possible. Exclusion diets such as of food colourings and additives may be of some value to a limited number of patients. Second- and third-generation low sedation H1 antagonists are the treatment of choice and improve many patients. Addition of an H2 antagonist or a mast cell stabilizing drug may provide additional benefit for a few. There are reports that leukotriene receptor antagonists improve some patients. Oral steroids are reserved if possible for severe exacerbation of chronic urticaria, and disabling pressure urticaria. Third-line therapies involving immunosuppressive agents are only appropriate for patients with chronic urticaria refractory to other measures, and usually autoimmune. The encouraging results using short courses of oral cyclosporin, high dose intravenous immunoglobulin and plasmapheresis need to be confirmed in placebo-controlled trials, in patients with or without demonstrable serum histamine releasing activity.

Novel therapeutic approaches in dermatology

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Drug research nowadays follows a clear path. Therapeutic Areas (TA) of interest are defined and interest is limited to an overseeable number of TAs. A scientific target such as signal transduction, anti-allergy or immunology is then identified. Biological target research and identification is then the next step and the key to successful development of a novel therapeutic.

Recent advances in identifying the human genome have helped in understanding some biological differences between disease and health. The real answer to this question, however, may lie in Protcomics. Being able to identify abnormal proteins purely associated with a disease state allows the precise targeting of this disease. Synthesizing a novel compound is then aided by computorial chemistry and preclinical testing is further aided by proteomics to evaluate toxicology. The resulting drug candidates will be specific for diseases and the target in question. The biology of what we see as a homogenous disease appearance may found to be different on an individual level. This is likely to result in personalized therapy according to the target rather than the disease or tumour histotype.

Novartis has focused on dermatology amongst other TAs and it is here as well as in other TAs that we exploit our target search capabilities to the full. However, we also apply technologies from other TA's (oncology, transplantation, asthma research). As part of this presentation, we will therefore present the development platforms tyrosine kinase inhibition, angiogenesis inhibition, anti-allergy research, biological skin and immunology. Lead compounds of possible relevance to dermatology in all areas will be presented and we will conclude in presenting some of the data of the most advanced compound, Elidel^{TM} (pimecrolimus).

Evaluation of SDZ-ASM 981 [ELIDEL^{TM} (pimecrolimus)] in a trial simulating clinical practice in managing childhood atopic dermatitis

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A multicentre clinical trial (Study B313), involving clinicians from countries across Europe, was designed to evaluate the possible role of SDZ-ASM 981 as one part of a long-term strategy in the management of childhood atopic dermatitis

(AD). The principal feature of the study was a therapeutic regimen in which SDZ-ASM 981 (or control base) was applied, in addition to routine emollients, to very early signs of inflammation. Topical corticosteroids were available in both arms for active flares of disease. 474 patients were recruited to the active arm and 237 patients to the control arm. The age-distribution, disease severity at baseline and other major parameters were identical in the two groups.

The primary end point of the study was the number of flares after 6 months of treatment. Secondary endpoints included the number of flares at 12 months, also flares assessed against disease severity at 6 and 12 months, the amount of topical corticosteroid used and the effect on Eczema Area and Severity Index (EASI). Safety parameters assessed included adverse events throughout the study, a physical examination and laboratory tests at baseline, 6 and 12 months, and skin recall antigen tests at the end of the study.

Of the patients who were enrolled, 24% had discontinued the study in the active arm at 6 months compared with 48% in the control arm. By 12 months these figures were 32% and 52%, respectively. The main reason for discontinuance was lack of efficacy (12% SDZ-ASM 981; 30% control). There were fewer flares at 6 and 12 months in the active arm than the control arm and the discontinuation rate correlated with the number of flares in the AD. The positive effect of SDZ-ASM 981 was seen in mild, moderate and severe AD. Patients in the SDZ-ASM 981 arm used substantially less corticosteroid than those in the control arm. There was a rapid and sustained improvement in EASI in the active arm, approximately twice as great as that seen in the control patients.

There was no significant difference in adverse events between the two groups and rates were similar for both bacterial and viral infections. There was no difference seen in the rate of local side-effects at the site of application of the creams. Skin recall antigen responses were comparable between the two populations at the end of the study.

This study has demonstrated a positive effect of SDZ-ASM 981 in controlling flares of AD in children, in all degrees of severity. The patients treated with SDZ-ASM 981 used less topical corticosteroid and there was no increase in local or systemic side-effects.

A randomized multicentre, parallel group, double-blind, vehicle-controlled study to evaluate the efficacy and safety of 1% SDZ ASM 981 cream in the long-term management of atopic dermatitis in children from 3 months to 23 months of age

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SDZ ASM 981 is a novel ascomycin macrolactam derivative developed for the treatment of inflammatory skin disease – especially atopic dermatitis. It specifically inhibits the release of inflammatory cytokines from T cells and has been formulated for topical use as a 1% cream. In order to assess the long-term safety and efficacy in children 3 months to 23 months of age, a multicentre, parallel group, double-blind vehicle-controlled 1-year study has been performed.

Thirty-nine investigators in seven countries recruited 250 patients aged between 3 months and 23 months with a diagnosis of atopic dermatitis based on the criteria of Williams *et al*. These patients were randomized to either 1% SDZ ASM 981 cream [Eldel^{TM} (pimecrolimus)] or corresponding vehicle cream (4 : 1 Elidel^{TM}: control allocation), to he applied to all affected areas. Treatment was twice a day according to need. Medium high potency topical corticosteroid was allowed as second-line medication to control refractory flares. After acute control of the flare the patient reverted to study medication to maintain control of the disease.

Disease management is defined as controlling atopic dermatitis by treating early signs and symptoms with 1% SDZ ASM cream in order to prevent exacerbation to an extent that treatment with a second-line topical corticosteroid medication is required. Primary efficacy analysis was conducted on the frequency of flares observed.

In addition, clinical signs and symptoms were recorded using the Eczema Area and Severity Index (EASI) subject assessment, Investigator's Global Assessment and pruritus severity assessment. Adverse events and local tolerability were also recorded.

The Study demonstrated the efficacy of Elidel^{TM} (pimecrolimus) vs. control. There was a statistically significant decrease in the number of flares in the Elidel^{TM} group compared with control. A rapid and sustained improvement in pruritis and a significant reduction in EASI scores were also observed in the Elidel^{TM} group. The requirement for a moderately potent topical steroid in the Elidel^{TM} group was decreased as compared with the control group.

Adverse events in both groups were similar with no significant systemic event. Infection – bacterial and viral – including the normal childhood illnesses, was similar in the two groups and application site adverse events were also similar in the two groups.

Management of necrobiosis lipoidica

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The significance of necrobiosis lipoidica includes its relationship to insulin dependent diabetes mellitus, its tendency to break down into painful ulcers, an – albeit rare – association with squamous cell carcinoma and, by no means least, its cosmetic impact, occurring as it does on the shins of young and middle-aged women. It is a degenerative disease of collagen in the dermis and subcutaneous fat but very little is known about its aetiology. The most popular theories are that it has a microangiopathic basis, is the result of vascular occlusion, is due to immune complex formation, or is a consequence of abnormal glucose transport by cutaneous fibroblasts. The histology of necroblosis lipoidica offers few

clues about aetiology and is characterized by a diffuse, tiered granulomatous dermatitis extending down to the panniculus, with palisades of histiocytes around zones of degenerated collagen bundles. With the passage of time, progression to sclerosis of the reticular dermis and subcutaneous fat occurs. In early lesions, a neutrophilic vasculitis may be evident.

In the absence of knowledge regarding the aetiology, there is at present no rational therapy for necroblosis lipoidica and our relative ignorance has spawned a wide variety of treatments over the years, most of which are of doubtful benefit but some of which appear to have potential. The majority of the literature on the treatment of necrobiosis lipoidica refers to anecdotal reports and there is a paucity of controlled trials. The main modalities of therapy include: nonspecific anti-inflammatory agents, such as topical, intra-lesional and systemic corticosteroids; drugs acting on the haemostatic mechanisms, such as an aspirin/dipyridamole combination and pentoxifylline; physical techniques, such as excision/grafting and laser surgery; enhancement of wound healing, such as hyperbaric oxygen, tissue-engineered human dermis, GM-CSF and becaplermin; and immunomodulatory drugs, such as cyclosporin and mycophenolate mofetil.

There has been a particular recent interest in photochemotherapy, with several different groups reporting the benefits of topical PUVA in both ulcerated and nonulcerated necrobiosis lipoidica. However, there have not as yet been any controlled clinical trials, and PUVA would lend itself to within-patient comparison. The cosmetic effect of tanning would need to be assessed and consideration given to the potential for increasing the risk of squamous cell carcinoma. The immunomodulatory property of PUVA may be a possible mechanism of its action.

Management of pyoderma gangrenosum

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Pyoderma gangrenosum (PG) is an idiopathic ulcerative condition of the skin. There are several clinical variants of this disorder that have been described, including classical, atypical, peristomal, and mucosal forms. In all forms pathergy is a common feature. Roughly 50% of the patients with PG will have an associated disorder, but the associations vary based upon the clinical variant of PG. Specifically, classical PG tends to be associated most commonly with inflammatory bowel disease or arthritis, atypical PG is associated with leukaemic and preleukaemic states, and peristomal PG is most often associated with inflammatory bowel disease has also occurred in patients with stomas created after cancer surgery. PG is a diagnosis of exclusion and therefore cultures and biopsies are generally part of the evaluation. Once a diagnosis is established, management begins with treatment of an associated disorder when present. For patients without an associated disease, or for those where the associated disease is controlled or quiescent, therapy often begins with systemic corticosteroids with or without an immunosuppressive agent. There are no controlled, randomized trials that demonstrate the effectiveness of any of our therapeutic approaches for these patients, therefore the therapeutic ladder is one of personal choice. This presentation will focus on diagnosis, evaluation and therapy.

Management of alopecia areata

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Alopecia areata is a common chronic inflammatory disease, which is probably mediated by lymphocytes. The predisposition to alopecia areata is polygenic in nature but environmental factors may trigger episodes of the disease. The diagnosis is usually not difficult and this presentation will concentrate mainly on patient management.

An explanation of alopecia areata, including discussion of the nature and course of the disease and the available treatments, is an important part of management. Overall, there is a high rate of spontaneous remission but almost all sufferers will experience more than one episode of alopecia and patients presenting to dermatologists tend to be affected more severely. Poor prognostic indicators include onset in childhood, failure of recovery within 1 year and extensive hair loss. The decision to treat alopecia areata actively should not be taken lightly. Treatment can be uncomfortable for the patient, time consuming and potentially toxic. Some patients find it difficult to cope with relapse following or during initially successful treatment and they should be forewarned of this possibility. On the other hand, some patients are appreciative that something has been tried, even if it does not work.

A number of treatments can induce hair growth in alopecia areata, but none has been shown to alter the natural history and few have been subjected to randomized controlled trials. Simple topical treatments include topical steroids, minoxidil lotion and dithranol although there is little evidence that the results are superior to placebo. Intralesional steroids stimulate hair growth in a high proportion of patients and can be helpful where hair loss is limited in extent or for certain sites such as the eyebrows. Several uncontrolled studies have suggested that pulsed high-dose systemic steroids are effective in some patients and this approach is possibly useful in rapidly progressive alopecia. The most effective treatment in severe alopecia is contact immunotherapy. However, the long-term response rate in this group of patients is low (15–20%), it is available in only a few centres and there are significant safety considerations for patients and carers.

Following sympathetic counselling no treatment is an active option for many patients with alopecia areata. Prescription of a wig can make the difference between social isolation and leading a normal life for patients with extensive hair loss. Finally, we have a responsibility to deter patients from indulging in a succession of useless and inevitably expensive ‘cures’.

Refractory hand dermatitis

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Hand dermatitis is often dismissed by medical practitioners as being trivial because of the limited area of skin involvement. However, the morbidity of sufferers is often not comprehended. All too often patients are not given the benefit of full investigation with appropriate treatment. Psoriasis localized to the hands is frequently misdiagnosed as hyperkeratotic eczema and requires potent treatment to clear. Fungal infections are also commonly overlooked.

The majority of hand dermatitis seen in the community is due to irritant contact factors. The importance of identifying all the factors relevant to irritation needs to be communicated to patients. Good hand care needs to be maintained for a minimum period of 3 months after recovery to prevent relapses from occurring. Common failures of response are due to inadequate usage of a potent enough steroid, lack of occlusion, and failure to apply emollients with enough frequency.

Any patient with hand dermatitis that has not responded after 4 weeks to advice on improved hand care combined with first-line treatment should be investigated for potential Type I and 1 V hypersensitivity. The pattern of involvement of the hands is often no clue as to causation. No patient should be told to change occupation without such investigations.

Primary occupations are often blamed for the cause of dermatitis but in reality secondary occupations and domestic exposure may be the real reason for lack of response to treatment.

Patients with resistant hand dermatitis may have to be considered for second line therapies including PUVA, cyclosporin, methotrexate and retinoids.

Suggested instruction sheet for patients with hand dermatitis

1 Hand washing: Use lukewarm water and a soap substitute (e.g. Wash E45, Aqueous cream, Emulsifying ointment). If your hands are dirty use a nonperfumed soap without tar or sulphur. The soap should be used sparingly and the hands thoroughly rinsed. Dry carefully with a clean towel, especially between the fingers. If soap is used this should be followed with the application of a non-perfumed moisturizer.

2 If your skin is dry use a nonperfumed moisturizer (e.g. E45 cream, Diprobase cream Neutrogena Norwegian Formula hand cream, Aqueous cream, Oily cream BP, Emulsifying ointment, Liquid Paraffin/White Soft Paraffin) as frequently as possible to restore a feeling of suppleness. As your skin improves the frequency can be reduced. You can use different ones at different times of the day with less greasy preparations used when undertaking paperwork.

3 Avoid contact with detergents and other strong cleansing agents.

4 Avoid contact with shampoo. Use plastic gloves or let someone else shampoo your hair or your children's hair.

5 Avoid contact with polish: metal, wax, shoe, floor, car, furniture and window polishes.

6 Avoid contact with solvents: white spirits, petrol, paraffin, turps, thinners and trichlorethylene (tric).

7 Do not peel or squeeze citrus fruits with bare hands: oranges, lemons, limes, satsumas.

8 Do not apply hair lotion, hair cream or hair dye with bare hands.

9 Wear warm gloves in cold weather.

10 Rings should not be worn for work or housework until the skin has been clear for 3 months. Never wash your hands with soap while wearing a ring. Keep the inside of rings clean (brush under running water).

11 For washing up use running water if possible keeping the temperature of the water low. Use long handled brushes rather than cloths. Always wear gloves when in contact with washing up liquid or detergents.

12 When gloves are worn, use PVC rather than rubber – preferably with cotton gloves inside to reduce sweating and friction. They should not be worn for more than 20 minutes at a time. If water happens to enter a glove, it should be immediately removed. Gloves should be turned inside out and rinsed under warm water several times a week. The outside gloves should be replaced every few weeks for home use and more frequently for industrial use.

13 Washing machines and dishwashers are an ideal way of preventing further attacks. Use a measure when handling detergent powder.

Remember that the resistance of the skin is lowered for at least 4 or 5 months after the dermatitis has apparently healed. Therefore continue to follow these instructions.

Management of dermatitis herpetiformis

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Dermatitis herpetiformis (DH) is a vesiculo-bullous disease with a characteristic clinical picture. The diagnostic hallmark is the demonstration by direct immunofluorescence of IgA deposits in the dermal papillae of uninvolved skin. The diagnosis should not be made without this finding.

Patients with DH have an associated gluten sensitive enteropathy and overwhelming evidence has been presented over the last 30 years that gluten causes both the rash and the enteropathy of DH in genetically predisposed individuals. Nearly all patients with DH have the histocompatibility antigens HLA B8 DR3 and DQw2 and associated target specific autoimmune disease. The management of DH has to be directed at control of the rash, identification of the severity and treatment of the associated gluten sensitive enteropathy and identification and treatment of associated autoimmune disease.

The rash of DH responds impressively to oral therapy with dapsone. Itching subsides within 24 h of starting treatment and new lesions stop appearing after 48 h. Cessation of

therapy leads to recurrence of the rash. The use of dapsone is limited by its side-effects. It is a powerful oxidizing agent and in therapeutic dosages of about 100 mg daily causes a chemical haemolysis. Elderly atherosclerotic patients will not tolerate even moderate degrees of haemolysis. Dapsone also has idiosyncratic side-effects such as headache and lethargy. These unwanted effects lead to withdrawal of dapsone therapy in about 25% of patients in whom it is prescribed and substitution with a sulphonamide such as sulphapyridine or sulphamethoxypyridazine, usually brings about adequate control. Once the rash is controlled it is important to establish the minimum drug requirements as many of the toxic side-effects are dose dependent.

The severity of the associated gluten sensitive enteropathy is variable ranging from symptomatic coeliac disease to a mild abnormality of permeability. Patients with DH should be placed on a strict gluten-free direct (GFD). After approximately 6 months the minimum drug requirements start to fall and patients are usually able to withdraw completely from drug therapy after about 2 years on the diet. The GFD controls the rash of DH regardless of the severity of associated enteropathy and has to be maintained indefinitely.

The most common autoimmune associations of DH are thyroid disease and pernicious anaemia. Annual monitoring of serum autoantibodies is important to identify patients at risk.

Management of epidermolysis bullosa acquisita

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By all accounts, epidermolysis bullosa acquisita (EBA) is a very rare chronic subepidermal blistering disease which involves the skin and mucous membranes. The disease can appear in childhood, but has a wide age range with no sex, racial or ethnic group predilection. There is an absence of family or personal history of any blistering diseases. There is a developing association of the HLA-DR2 allele and some of these cases can have enhanced susceptibility to bullous SLE. Other disease associations with EBA include inflammatory bowel disease, amyloidosis, myeloma, thyroiditis, diabetes and multiple endocrinopathy syndrome.

EBA often presents with skin fragility and blistering that is usually trauma induced, so that the elbows, knees, knuckles, fingers and fingernails tend to be affected. The lesions heal with scarring and milia formation. However, some cases of EBA can have a clinical phenotype, similar to bullous pemphigoid, with widespread inflammatory vesicles and bullae. Other cases may present similarly to cicatricial pemphigoid with involvement of the eyes, mouth and genital areas. The severity of EBA varies, indicating a rather heterogenous nature. Milder cases undoubtedly occur and some of these go into spontaneous remission, but very severe cases can lead to blindness, oesophageal strictures and anal stenosis and be very incapacitating. The diagnosis of EBA can be confirmed by salt-split immunofluoresence procedures where the BMZ antibodies bind to the dermal side of the split. Ideally, one wishes to identify type 7 collagen by Western blot analysis, ELISA or immunoelectron microscopy.

EBA can be a very frustrating and difficult disease to treat. In our experience, EBA can show great heterogeneity in the response to therapy. Some cases appear mild and respond to low dose prednisolone with dapsone, 50–100 mg daily. More moderately severe cases require prednisolone, azathioprine or cyclosporin. There are, undoubtedly, very severe cases which appear to be resistant to all of the above therapies. It is not advised that very high dose oral corticosteroids he administered in EBA, as often this is ineffective and leads to crippling steroid side-effects. For very resistant or severe cases, the use of oral mycophenolate mofetil can be recommended. Some cases may respond to IV pulses of prednisolone and cyclophosphamide and others, to IVIG infusions. Unfortunately, because of the rarity of the disease, no exact therapeutic policy has been established and each case requires consideration on its merits. Management of cases with severe ocular, oesophageal or genital involvement is best done within a specialized centre which includes facilities for endoscopic techniques for strictures.