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CORRESPONDENCE

Are we going OTT about ITT?

SIR, The recent editorial by Hywel Williams[1] on intention-to-treat analysis (ITT) brings to mind the remarks made by the distinguished American epidemiologist and biostatistician, Alvan Feinstein, when referring to the folly of ITT: in an attempt to exclude bias we have excluded common sense.[2,3] Hywel Williams favours the conventional wisdom, at least amongst epidemiologists and some biostatisticians, that a clinical trial by way of some form of naive inductionism tells one how to treat patients. I disagree, and suggest it is better to think of a clinical trial as a natural experiment that allows one to test a hypothesis, a hypothesis that then informs clinical practice.

Imagine an experiment in a genetics laboratory. You wish to see whether a certain species of messenger RNA is expressed in a sample of RNA from a particular tissue. You add various enzymes, some oligonucleotide primers, some substrate and the target RNA. The mixture is then incubated at an appropriate temperature. If all goes according to plan, when you run an aliquot of the finished reaction out on a gel you will see whether a band is present. Imagine however, that while you are out of the laboratory, somebody comes in and changes the temperature of your incubator. The result is that the enzyme is unable to work appropriately and the specificity of your primers is changed. In either case the results are erroneous. Now, of course, you can argue that organisms live at various different temperatures, that global warming may be occurring, that many people spend lots of time in sweaty and hot nightclubs and so on… Most biologists, however, just chuck the results out and do the experiment properly. Not the ITT trialist however.

Science consists of taking the world apart and testing it under highly artefactual circumstances.[4] Experimentation isn't a facsimile of the natural world, for the simple reason that if it were, we couldn't interpret it. Without simplification and reductionism we can't understand the external world.[5] Instead, science sets tests to see how nature behaves: question and answer; no carbon copies. When viewed this way, ITT can be seen to portray a mistaken view of the scientific enterprise. It is the pertreatment protocol that is the one that tests the hypothesis and that provides coherent biological insight. How you extrapolate from the results of a trial to how you treat patients is a distinct and of course important issue.

The idea of naive inductionism as a way of obtaining knowledge about the external world was killed by David Hume over 200 years ago.[5] The only way you can extrapolate data from an experiment performed yesterday, to the patients you see tomorrow, is by some sort of coherent theory to explain events. It is that theory that we must test in an experiment. Patients in clinical trials are rarely typical patients, they are virtually never randomized from a defined target population and of course they are not treated as in normal clinical practice. Trials don't, nor should they, mirror the everyday. The idea of a pragmatic experiment is a logical error: you have not got an experiment, rather just a photocopy of reality, which will not be understandable until the image is translated into a form the mind can manipulate.

These epistemic issues are not esoteric, or at least should not be to those interested in skin disease. I am sure I am not the only one who has watched major pharmaceutical companies abandon development of a compound for the treatment of skin disease simply because of the results analysed by an ill-advised ITT analysis.

Hywel's comments about the PASI score are well taken but of course betray the very points he seeks to make. What clinician is surprised by what he says? Trials, like good experiments, test ideas: it is ideas that then guide the hand of action, not summary statistics.

Department of Dermatology J.R. REES
Royal Infirmary of Edinburgh,
Lauriston Building Lauriston Place
Edinburgh EH3 9YW, U.K.
E-mail:
jonathan.rees@edinburgh.ac.uk

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Are we going OTT about ITT? Reply from author

SIR, Randomized controlled trials (RCTs) have many limitations. Yet despite portraying me as some kind of fanatical reductionist zealot who blindly obeys summary statistics, my friend Jonathan Rees will find me agreeing with him over many of his views about the difficulties of generalizing from trials to patients.[1] In his haste to criticize RCTs, Jonathan makes a basic error in confusing internal validity of a trial (i.e. are the results true?) with external validity (i.e. how generalizable are the results to the patients that I treat?).

As I have failed in my task of explaining the principle of ITT, I will try again, this time by reflecting the very genetics example that Jonathan proposes (even though I prefer to talk about people when talking about people). If someone had interfered with the gels that he refers to by altering the incubation temperature, then the conditions of that experiment would have been seriously breached and the

experiment should be abandoned. The parallel situation in a clinical drug trial would be an instance whereby it is discovered that the drug under test has been inactivated by hot storage conditions. I doubt if any person would be stupid enough to analyse and present that data under such a violation. This is *not* the same as ITT.[2] Now, supposing that amongst 12 gels that Jonathan runs, two do not show the results that fit in with his preconceived ideas of what the results should show. Does he exclude them from his analysis? Of course not. This, in effect, is what ITT is all about; accounting for *all* those who have been entered into an experiment in a fair and sensible way. In simple English, it is a way of reducing cheating.

People who drop out of trials are systematically different from those who remain in them in a number of ways.[3] People may drop out because they drop dead, encounter unacceptable adverse events, they may get worse (or no better), or simply because following the proposed regimen is too much of a palaver.[4] They may even drop out because the treatment works so well. Ignoring them is not acceptable. The moment one makes *post hoc* judgements about excluding those who drop out after the crucial step of randomization, then one is potentially biasing the results. The purpose of randomization in the first place was to compare like with like on an even playing field.

Jonathan's assertion that many a potentially useful drug has been dropped because of an inappropriate ITT analysis is simply not true. This was exactly the point I was trying to make in citing the example of a new topical drug for acne with good efficacy but unacceptable irritancy; an efficacy analysis of just those who completed might provide useful information to the sponsor of the potential benefit of the drug and the need to go back to the drawing board to try and reduce irritancy. This is what Phase II trials are all about, where per protocol analyses are desirable and informative. Per protocol analyses are also desirable in trials that seek to demonstrate therapeutic equivalence for other more complex reasons.[5]

I disagree with Jonathan that all clinical trial results only give clinicians ideas about treatments. Well-designed large clinical trials that include those whom we wish to treat can tell us all sorts of useful things such as likely magnitude of effect, how a treatment compares with existing treatments, who might respond best and in what way in terms of cost and adverse effects. This is one reason why the drug industry invests billions of dollars each year in conducting Phase III trials instead of just stopping after a case report or small Phase II study.

Clinical trials certainly have their limitations, but if I am ever taken seriously ill, I would prefer to be guided by the results of a well-conducted trial than the 'hand of action' that Jonathan proposes. History has shown us how our 'hand of action' has occasionally been responsible for the use of leeches, blood-letting, deep insulin coma for malaria, mutilating operations for breast cancer, 10-cm excision margins for early melanoma and vulvectomy for lichen sclerosus. Until better designs come along for informing clinical practice in a truthful and helpful way, I will continue to be guided by clinical trials, especially those that use an ITT analysis. I will retain a healthy scepticism of such trials, especially as our record of quality trials in dermatology has not been too good to date.[6] I appeal to Jonathan Rees to work with me to try and improve the current state of affairs and not to go backwards in history in despair.

Centre of Evidence-Based Dermatology H.C. WILLIAMS
Queen's Medical Centre
University of Nottingham
Nottingham NG7 2UH, U.K.
E-mail: hywel.williams@nottingham.ac.uk

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Extragenital lichen sclerosus successfully treated with topical calcipotriol: evaluation by *in vivo* confocal laser scanning microscopy

SIR, Lichen sclerosus (LS), originally described by Hallopeau in 1887, is an uncommon skin disease with white porcelain-like sclerotic skin lesions predominantly affecting the anogenital area. Extragenital LS mostly occurs on the flexor surface of the wrists, the upper part of the trunk, and in the axillae.[1] LS is more common in adult women, but may also occur in men and children. To date, there is no standardized treatment for LS. In some patients, potent topical corticosteroids may improve lesions; in others, various treatments including topical testosterone and oestrogen, psoralen plus ultraviolet (UV) A, penicillin, resorcinol, chloroquine, vitamins and retinoids have been used with variable success.[2,3] We recently reported the successful treatment of patients with localized scleroderma by long-wave UVA1 (340–400 nm) phototherapy and topical calcipotriol.[4] Because of similar clinical and histopathological features of localized scleroderma and LS, we hypothesized that topical calcipotriol may also improve extragenital LS. We report a patient with extragenital LS that responded well to monotherapy with calcipotriol ointment.

A 69-year-old caucasian woman presented with a 9-month history of sclerotic skin lesions. Her medical background was unremarkable. Examination showed hypertrophic indurated plaques on the back (Fig. 1a). The genital region was not affected. *In vivo* confocal laser scanning microscopy (Vivascope 1000; Lucid, Henrietta, TX, U.S.A.) revealed compact hyperkeratosis (37 μm compared with 15 μm in uninvolved skin) and an increased epidermal thickness (minimal epidermal thickness of 78 μm compared with 48 μm in uninvolved skin). The papillary dermis showed decreased interdigitation with the epidermis, marked sclerosis and a homogeneous appearance of the collagen. No blood flow was observed down to 150 μm beneath the surface.

A punch biopsy from an affected area showed basal cell liquefaction, oedema and pallor of the upper dermis and a band-like lymphohistiocytic infiltrate, features consistent with LS. *Borrelia*-specific DNA was not detected in lesional skin by polymerase chain reaction and *Borrelia* serology was negative. Laboratory investigations revealed no evidence for systemic disorders, in particular autoimmune diseases.

Local therapy consisted of calcipotriol ointment 0·005% (Daivonex®) twice daily (applied under occlusion in the morning and evening) for 12 weeks. The amount of calcipotriol ointment used was restricted to a thin layer to the affected areas (1·5 g to a 10-cm^2 area). No side-effects were observed during the treatment period. Three weeks after beginning therapy, the number of hypertrophic plaques had decreased markedly. After 40 treatment sessions, almost all skin lesions had resolved (Fig. 1b). At this time, *in vivo* confocal laser scanning microscopy revealed mild hyperkeratosis (19 μm; uninvolved skin 15 μm), no epidermal hypertrophy and less marked dermal sclerosis. The epidermal–dermal interdigitation showed no changes from the first investigation, but there was blood flow visible in horizontally orientated dermal vessels (not yet in vertically orientated capillary loops as in uninvolved skin sites). The clinical improvement was sustained over a 6-month follow-up period.

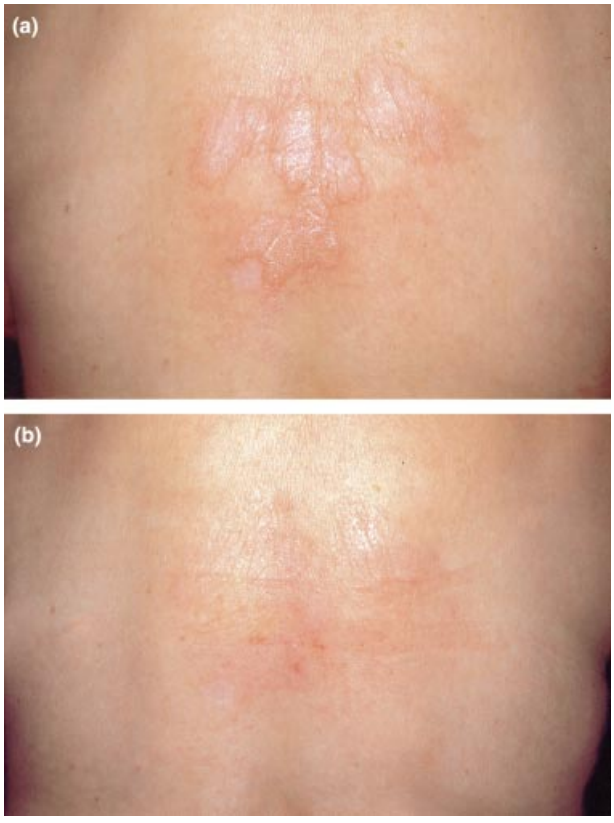

Figure 1. (a) Hyperkeratotic plaques on the back. (b) Almost complete resolution of skin lesions after 12 weeks of treatment with calcipotriol ointment.

Calcipotriol ointment has been reported to be an effective and safe treatment for long-term use in childhood plaque-type psoriasis.[5] The effectiveness of calcipotriol in morphoea may be due to alteration of collagen and fibronectin synthesis and to inhibition of fibroblast proliferation. Morphoea fibroblasts may have an increased sensitivity to vitamin D_3 receptors, leading to inhibition of proliferation.[6,7] Because of distinct clinical and histological similarities between localized scleroderma and LS, topical calcipotriol may be effective in LS by the same mechanism. The precise pathway remains to be clarified. In the present case, clinical improvement of hypertrophic LS was confirmed by *in vivo* confocal laser scanning microscopy. Topical calcipotriol seems potentially to be an effective treatment option for the management of LS. Controlled studies, especially on more atrophic forms of LS, are, however, necessary to substantiate our promising initial findings.

Department of Dermatology,
Ruhr-University Bochum,
Gudrunstrasse 56, D-44791
Bochum, Germany
E-mail: A.Kreuter@derma.de

A. KREUTER
T. GAMBICHLER
K. SAUERMANN
T. JANSEN
P. ALTMEYER
K. HOFFMANN

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Dermatological complications of etanercept therapy for rheumatoid arthritis

SIR, Etanercept is a fusion protein consisting of the extracellular ligand-binding domain of the 75-kDa receptor for tumour necrosis factor (TNF)-α and the constant domain of human IgG1. This new drug is administrated by subcutaneous injection for the treatment of rheumatoid arthritis and will be probably used in other autoimmune diseases such as psoriasis, and even in chronic heart failure.[1] Until now, the known adverse events have mainly been infections (of the upper respiratory tract in particular) and injection-site reactions.[1,2] We report new dermatological adverse events.

Patient 1. A 57-year-old woman suffering from rheumatoid arthritis was treated with etanercept (Enbrel®; Immunex Corp., Seattle, WA, U.S.A.). She developed a rash after her second injection. A patch of erythema with follicular hyperkeratosis occurred at the injection site, and other similar lesions developed at non-injection sites. Skin biopsy revealed discoid lupus-like lesions of folliculitis. The patient had no history of lupus. Antinuclear antibodies were present (1 : 40) but there were no anti-DNA antibodies. Treatment with etanercept was not discontinued. The lesions did not disappear but were greatly attenuated. The titre of antinuclear antibodies did not increase after 6 months of treatment.

Patient 2. A 47-year-old woman with seronegative but HLA-DRB1*0401+ rheumatoid arthritis was treated with etanercept. After the first injection, a single necrotic patch (5 × 7 cm) appeared on the right leg (Fig. 1). The treatment was stopped but a widespread eruption of severe purpuric and necrotic lesions occurred on the lower limbs. Skin biopsy revealed necrotizing vasculitis. A monoclonal IgG κ cryoglobulinaemia was detected. There was no renal involvement. The patient was treated with cyclophosphamide. After three boluses, the cutaneous lesions disappeared and the cryoglobulinaemia decreased but did not disappear over a follow-up period of 14 months.

Patients developing antietanercept antibodies or autoantibodies (antinuclear, anti-DNA or anticardiolipin antibodies) have been reported previously.[1] Until now, associated autoimmune diseases have rarely been reported.[3] To our knowledge, we report the first cases of discoid lupus and cryoglobulinaemia developing during treatment with etanercept. Etanercept is a new product and long-term studies are required to determine its ultimate effects on the occurrence of autoimmune diseases. Etanercept and other TNF-α inhibitors bring marked improvement in several diseases, especially rheumatoid arthritis. However, the use of biological therapies for modulation of the cytokine disequilibrium observed in rheumatoid synovitis may also have undesirable effects on the systemic adaptive immune response.

The mechanism of action of etanercept is competitive inhibition of TNF-α binding to cell-surface receptors, preventing TNF-α-mediated cellular responses by rendering TNF-α biologically inactive. The pathway whereby this drug may induce autoantibody production and autoimmune disease remains unclear. Etanercept acts on inflammation but does not modify global production of immunoglobulins.[4] It might disrupt the idiotypic network. Alternatively, an increase in interleukin 10 might contribute by increasing autoantibody production.[5]

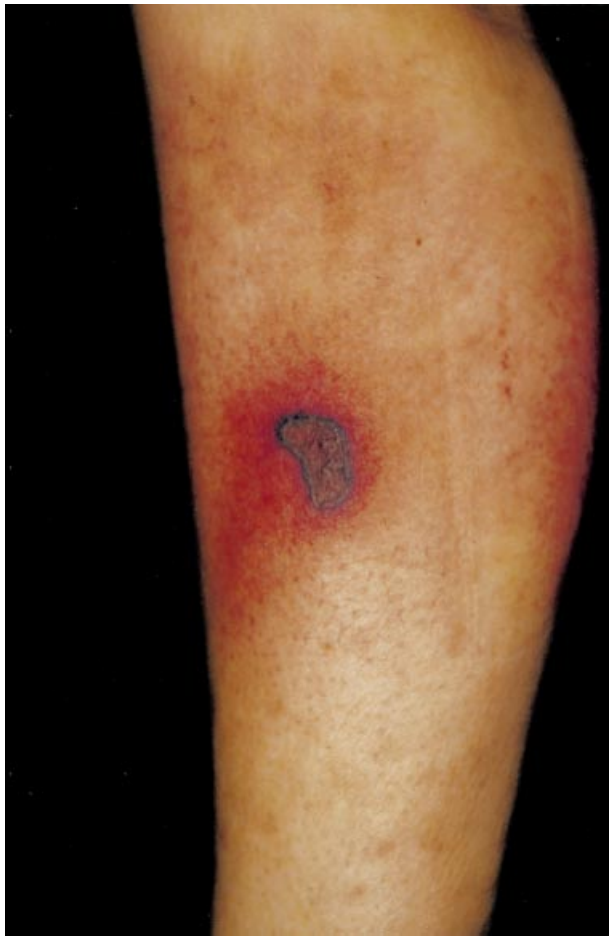

Figure 1. Patient 2: necrotic lesion on the leg after one injection of etanercept (this is not the injection site).

Departments of Dermatology, L. MISERY
**Pathology and †Rheumatology,* J-L. PERROT
Hôpital Nord, A. GENTIL-PERRET*
42055 Saint-Etienne cedex 2, France B. PALLOT-PRADES†
E-mail: laurent.misery@ F. CAMBAZARD
univ-st-etienne.fr C. ALEXANDRE†

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Treatment of severe psoriasis and psoriatic arthritis with leflunomide

SIR, Psoriasis is a chronic inflammatory skin disease with T cells and neutrophils infiltrating both the dermis and epidermis, and excessive scaling related to epidermal hyperproliferation. Psoriatic arthritis, i.e. concurrent inflammation of joints, bones and ligaments, is present in up to 20% of affected patients. The psoriatic inflammatory process is associated with characteristic changes in the cytokine network that are believed to play a major part in disease pathophysiology. Over-expression of proinflammatory T-helper type 1 cytokines such as tumour necrosis factor-α and interferon-γ and a relative deficiency of anti-inflammatory factors such as interleukin (IL)-10 and the IL-1 receptor antagonist (IL-1Ra) are observed in lesional and lesion-free skin, peripheral blood mononuclear cells and the synovium of inflamed joints.[1,2] Leflunomide is a novel immunomodulatory drug that has been licensed for the treatment of active rheumatoid arthritis in several countries including the U.S.A. and several in Europe. The active metabolite of leflunomide, A77 1726, inhibits proliferation of activated T and B cells mainly through inhibition of protein tyrosine kinases and the enzyme dihydroorotate dehydrogenase that is involved in the *de novo* synthesis of pyrimidine nucleotides.[3] Other *in vitro* activities of A77 1726 include the modulation of cytokine production in T cells and neutrophils, suppression of immunoglobulin synthesis in B cells and reduction of mononuclear cell adhesion, suggesting a therapeutic potential in a broad range of inflammatory and autoimmune disorders. We report the successful treatment with leflunomide of a patient with severe recalcitrant pustular psoriasis and psoriatic arthritis.

A 56-year-old woman with a 44-year history of psoriasis vulgaris and a 15-year history of severe mutilating peripheral polyarticular psoriatic arthritis presented with an exacerbation of skin and joint symptoms. She had received methotrexate 7·5 mg weekly for 9 years until 6 months previously, when liver function test revealed early liver cirrhosis. Cyclosporin 2 mg kg^{-1} daily was started, but was ineffective and had to be stopped after 6 months because of a deterioration of renal function. Our patient had extensive plaque psoriasis affecting at least 30% of the body surface, and painful swellings of the finger joints. Systemic prednisolone 1 mg kg^{-1} daily was started (tapered to 10 mg daily), together with sulphasalazine (final dose 2 g daily). In addition, psoralen plus ultraviolet A (PUVA) bath photochemotherapy was initiated in combination with topical vitamin D_3 analogues and corticosteroids. Two months later, our patient developed subacute generalized pustular psoriasis with pinpoint pustules arising on pre-existing plaques and a spread of erythema and pustulation to previously unaffected areas, particularly the flexures and genital region. Pustular skin eruptions on the trunk and extremities were accompanied by massive palmoplantar pustulosis (Fig. 1a) and an exacerbation of polyarticular arthritis of both hands and feet. Leflunomide (Arava®, Hoechst Marion Roussel) 10 mg daily was added to the therapeutic regimen. Because of the preexisting hepatopathy, our patient received no loading dose and liver enzymes were monitored at close intervals. Three weeks later, joint swelling and articular pain had almost completely resolved and there was a striking improvement of pustular skin lesions (Fig. 1b). During the following weeks PUVA therapy and sulphasalazine were stopped. Six months later our patient's condition is still well controlled on leflunomide 10 mg daily, prednisolone 10 mg daily and topical vitamin D_3 analogues. Renal and liver function have remained stable throughout the treatment.

Leflunomide may suppress the psoriatic inflammatory cascade at multiple levels. A77 1726 inhibits nuclear factor κB-dependent gene transcription,[4] which is thought to contribute to the over-production of several proinflammatory cytokines involved in psoriasis. Conversely, A77 1726 upregulates production of IL-1Ra in monocytes[5] and increases epidermal cell expression of the IL-10 receptor,[6] two components which are decreased in psoriatic skin lesions. Finally, there is evidence that leflunomide inhibits epidermal cell

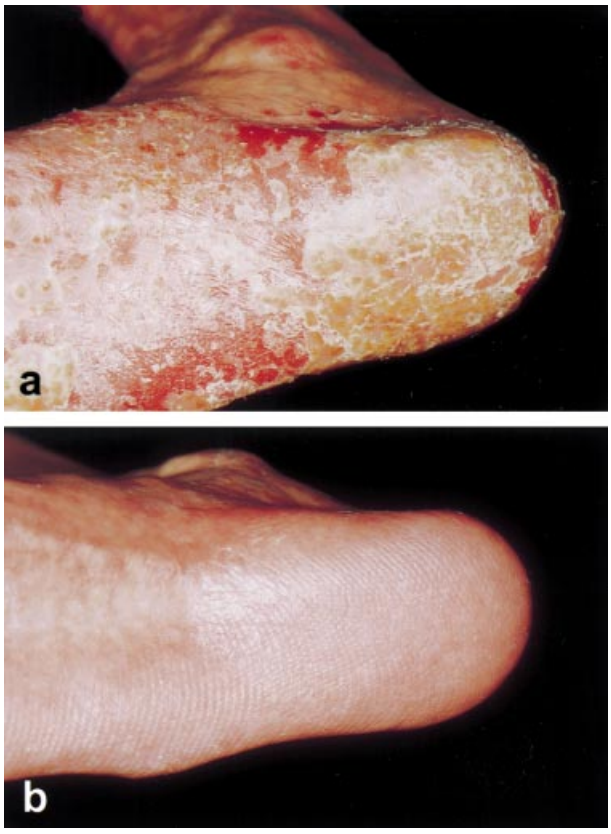

Figure 1. Clinical aspect of plantar pustular psoriasis before (a) and after (b) 3 weeks of treatment with leflunomide 10 mg daily.

proliferation through induction of the negative cell cycle regulator *p*53.[6] These findings add to the rationale of a therapeutic application of leflunomide in psoriasis. Our report suggests that leflunomide may be effective even in severe cases of psoriasis and psoriatic arthritis recalcitrant to other immunosuppressive agents and encourages clinical studies in these indications.

Departments of Dermatology and K. REICH
**Nephrology/Rheumatology,* K. M. HUMMEL*
Georg-August-University, I. BECKMANN
Von-Siebold-Strasse 3, R. MÖSSNER
37075 Göttingen, Germany C. NEUMANN
E-mail: kreich@gwdg.de

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Treatment of erythromelalgia with a serotonin/noradrenaline reuptake inhibitor

SIR, Erythromelalgia is an unusual disorder characterized by the triad of red, hot and painful extremities. The symptoms are exacerbated by heat and improved by cold. Its aetiology is not fully understood. Numerous different medications including aspirin, gabapentin, amitriptyline, benzodiazepines and opiates have been used in attempts to treat the symptoms of erythromelalgia, with varying success.[1] We report our experience with the use of venlafaxine (Efexor®; Wyeth-Ayerst Pharmaceuticals, St Davids, PA, USA), a serotonin and noradrenaline reuptake inhibitor, in the treatment of primary erythromelalgia. Venlafaxine has previously been reported to improve the symptoms in one case of Raynaud's phenomenon[2] and two cases of erythromelalgia.[3]

Ten patients with primary erythromelalgia were studied. Appropriate investigations were performed to exclude associated causes. Patients were subsequently treated with oral venlafaxine 37·5 mg twice daily. The patients were examined weekly for evaluation of symptoms, as well as for severity and extent of skin warmth and erythema.

All patients were able to tolerate the treatment without major side-effects. Following 1 week of therapy, a marked improvement in pain and burning was reported by all patients. There was also an appreciable decrease in the warmth and erythema in all patients. The most common side-effect was nausea, reported in two patients. The patients continued the treatment for up to 6–18 months with continued benefit, and no adverse reactions.

Primary erythromelalgia is a rare condition, usually diagnosed clinically, based on history, signs and symptoms. Investigation to exclude associated medical conditions, particularly myeloproliferative disorders, is required. Microscopic evaluation of skin biopsies is not always diagnostic. The pathogenesis of primary erythromelalgia is not entirely known.[1,4–6] A localized defect in the vascular and neural function of the involved skin has been proposed.[6] Arteriovenous shunting in the affected skin, with subsequent hypoxia and metabolic deficit, may play a significant role.[4] Inhibition of serotonin uptake by platelets has been shown to decrease platelet function and reduce platelet plug formation under shear stress.[7,8] We hypothesize that venlafaxine exerts its therapeutic benefit in erythromelalgia in part through this mechanism. The vasoactive properties of serotonin are not clearly understood, and the potential effects of serotonin reuptake inhibitors on the microvasculature are not known.[3] Histological examination of erythromelalgia skin has shown a decrease in the sympathetic innervation and deficient sympathetic regulation in the affected skin.[4,9] The implications of this decreased sympathetic innervation in the pathogenesis of erythromelalgia are not evident. Venlafaxine has been shown to inhibit noradrenaline uptake,[10] which may be an additional mechanism of action in erythromelalgia. Therefore, via its influence on noradrenaline as well as serotonin, venlafaxine may have dual efficacy in treating the underlying neurovascular phenomenon involved in erythromelalgia, rendering a therapeutic advantage over other selective serotonin reuptake inhibitors.

Venlafaxine has been used for the treatment of depression, anxiety and obsessive-compulsive disorders.[10] It has a low affinity for muscarinic, histaminergic and α1-adrenergic receptors, and has a low side-effect profile. The most common side-effects include nausea, somnolence and dry mouth, which decrease in severity with long-term therapy.[3,10] The recommended starting dose of venlafaxine for depression is 37·5 mg twice daily, and may be increased up to 375 mg daily.[10]

The results of this pilot study indicate that venlafaxine may be a safe and effective therapeutic option for patients with primary erythromelalgia. A placebo effect cannot be ruled out. This study is also limited by the small patient numbers and the lack of an objective measure of clinical improvement such as blinded assessment of photographs.

A double-blind placebo-controlled randomized study is under way; however, it has been limited by the low incidence of this disorder.

Wayne State University, 4201 St Antoine, Detroit, MI 48201, U.S.A. A. MOIIN
**Henry Ford Health System* S.S. YASHAR*
Dermatology Department and J.E. SANCHEZ†
‡UCLA Department of Biology, B. YASHAR‡
2799 W. Grand Blvd. K-16, Detroit, MI 48202, U.S.A.
†Western University of Health Sciences, 5530 manton, Woodland Hills, CA 91367, U.S.A.
Correspondence: Sharam S.Yashar.
E-mail: syashar@eudoramail.com

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Lack of modification of virological status after chemotherapy or radiotherapy for classic Kaposi's sarcoma

SIR, The role of human herpesvirus 8 (HHV8) is well documented in all epidemiological forms of Kaposi's sarcoma (KS), especially the classical form. Therapies usually advocated in this form include radiotherapy, chemotherapy and interferon.[1] We have studied the evolution of virological status in six patients with classical KS before and after chemotherapy or radiotherapy in order to assess whether or not clinical remission of the disease is associated with modification of this status.

Six patients with classical KS, five men and one woman, aged 45–95 years, were included in this study. One patient received chemotherapy and three, radiotherapy and chemotherapy for disseminated disease; two received radiotherapy alone for localized disease. Complete response, defined by disappearance of all visible lesions, occurred in five patients, and partial remission in one. In two cases, complete clinical response was confirmed by histology.

HHV8 DNA was searched for in lesional skin, non-lesional skin and peripheral blood mononuclear cells (PBMC) using a specific nested polymerase chain reaction technique as previously described.[2] A KS skin sample was used as positive control. Amplification products were visualized by agarose gel electrophoresis and the sequence confirmed by hybridization with a specific probe. The presence of circulating anti-HHV8 antibodies was detected by an HHV8 immunofluorescent assay (Biotrin, Ireland) using a latency protein of the virus. Both tests were performed before and 1–2 months after the end of treatment.

Before treatment, HHV8 DNA was detected in lesional skin in all patients and in none of the non-lesional skin samples (Fig. 1). HHV8 DNA was present in PBMC in two of four patients tested. The serological test was positive in all of the patients tested. After treatment, HHV8 DNA was detected in five of six postlesional skin samples, whereas one non-lesional skin sample was positive. It was also present in PBMC in three of the four patients. Serological analysis remained unchanged. These results, summarized in Table 1, were obtained regardless of the clinical response to treatment.

An aetiological role of HHV8 in KS is very likely. HHV8 DNA was observed in all our patients in lesional skin of classical KS, as reported in previous series. In normal skin, only one sample gave a positive result. In the literature, the percentage of HHV8 DNA detection in normal skin varies between 7% and 89%. HHV8 DNA is detected in PBMC in

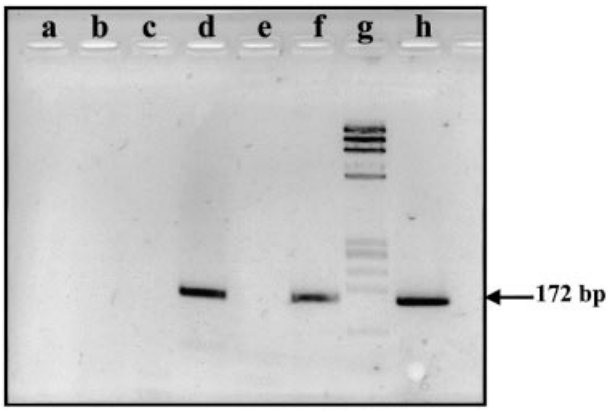

Figure 1. Patient 2: nested polymerase chain reaction (PCR) on normal skin and lesional skin, before and after treatment. Lane a, negative control; lane b, amplification of the negative control produced from a previous first round of PCR; lanes c and e, normal skin; lane d, lesional skin before treatment; lane f, lesional skin after treatment; lane g, DNA ladder (Gibco); lane h, positive control.

Table 1. Presence of human herpesvirus 8 before and after treatment

Patient no.		Lesional skin	Normal skin	PBMC	Serology
1	Before	+	–	+	ND
	After	+	+	+	ND
2	Before	+	–	–	1: 640
	After	+	–	–	ND
3	Before	+	–	–	1: 1280
	After	+	–	+	1: 1280
4	Before	+	–	+	ND
	After	+	–	+	1: 2560
5	Before	+	–	ND	1: 160
	After	–	–	ND	1: 160
6	Before	+	–	ND	1: 1280
	After	+	–	ND	ND

PBMC, peripheral blood mononuclear cells; ND, not done.

about 50–70% of cases. Our results are consistent with these data. Serological studies revealed the presence of anti-HHV8 antibodies in 80–100% of patients.[1]

Our results show that treatment of KS with chemotherapy or radiotherapy does not modify the rate of serum anti-HHV8 antibodies and that viral DNA is still present in skin and PBMC of patients with classical KS despite clinical remission. It is possible that a reduction in viral load is sufficient to achieve a clinical response, but the method used in this study does not allow any quantitative evaluation of the viral load. These results are in line with data obtained after treatment of classical KS with interferon-alfa by Deichmann *et al.*[3] and by Pfrommer *et al.*,[4] where remission was obtained but HHV8 DNA was still detected in postlesional skin[3] or PBMC.[4] It is possible that the persistence of the virus in skin and/or PBMC contributes to the relapses often observed after treatment.

Currently, the therapeutic strategy in KS is based upon destructive methods or cytotoxic drugs. However, recent advances in the treatment of AIDS-associated KS have shown that antiretroviral treatment using proteinase inhibitors completely clears clinical lesions and produces an undetectable viraemia,[5,6] suggesting that in immunodeficient patients, restoration of immune status can be followed by a disappearance of HHV8 in PBMC and/or lesional skin.

Another way forward for KS treatment could be the use of antiherpesvirus molecules. Foscarnet, ganciclovir and cidofovir inhibit HHV8 replication *in vitro*,[7,8] and Fife *et al.*[9] reported a clinical remission of KS after cidofovir treatment *in vivo*. Unfortunately, the HHV8 DNA status remained unchanged in the skin. The persistence of HHV8 in PBMC of patients treated with antiherpesvirus drugs has also been reported,[10] suggesting that classical antiherpesvirus drugs may not completely suppress expression of HHV8. Further studies with other antiherpesvirus molecules are required to determine their exact place in the treatment of KS. In the meantime, conventional therapies remain useful in patients with KS, giving significant clinical response even though the the frequent relapses might be explained by persistence of HHV8.

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Service de Dermatologie, Hôpital Saint Eloi, CHU Montpellier, 34295 Montpellier cedex 5, France
**Laboratoire de Virologie, CHU de Nimes, 30029 Nimes cedex 4, France*
E-mail: b-guillot@chu-montpellier.fr

B. GUILLOT
M. J. CARLES*
V. FOULONGNE*
O. DEREURE
M. RAMUZ*

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Porokeratosis of Mibelli: successful treatment with 5% imiquimod cream

SIR, We report a patient with porokeratosis of Mibelli that was successfully treated with topical imiquimod 5% cream (Aldara®; 3M, Loughborough, U.K.), a topical immunomodulator. A 55-year-old man was referred with a lesion on the right leg. The lesion was circular, 3 cm in diameter, with a keratotic rim and central atrophy (Fig. 1a). A clinical diagnosis of porokeratosis of Mibelli was confirmed by an incisional skin biopsy from the edge of the lesion. The epidermis showed

hyperkeratosis with the characteristic column of parakeratotic cells – a 'cornoid lamella'. The lesion was treated with imiquimod cream once daily for 5 days per week. After 3 months no clinical improvement was seen. Following this, imiquimod cream was applied once daily for 5 days per week under occlusion with an adhesive polythene dressing (Tegaderm®; 3M). Within 3 weeks the lesion had become inflamed with erythema and induration. Treatment was continued for a further 2 weeks and resulted in clearance of the lesion (Fig. 1b). Clinical examination 1 year later showed no evidence of recurrence, and a repeat biopsy showed complete histological resolution.

Porokeratosis was initially described independently by Mibelli[1] and Respighi[2] in 1893. Subsequently, several clinical variants were recognized based on different distribution patterns. In the classical porokeratosis of Mibelli, large annular keratotic plaques occur with a thread-like furrowed border. It is probably beneficial to treat lesions of porokeratosis of Mibelli not only for cosmetic reasons but also because of the risk of malignant transformation. This has been reported to be as high as 7·5% in a series of 200 patients.[3] Treatment of porokeratosis is notoriously difficult although a wide variety of treatment regimens has been described. Treatments include keratolytics, topical 5-fluorouracil,[4] etretinate,[5] carbon dioxide laser,[6] cryosurgery, electrocautery and excision. While surgical excision is the most definitive approach, this can be technically difficult in some cases, depending on the site, size and number of lesions. It is recognized that immunosuppression may favour the development of porokeratotic lesions.[7,8] T-helper (Th) 1 cells are the principal cells required in immune surveillance, and imiquimod has been shown to induce cytokines such as interferon (IFN)-γ, IFN-α, tumour necrosis factor-α and interleukin 12, which promote a Th1-type cell-mediated immune response.[9,10] The lack of response without occlusion would suggest that imiquimod cream is unable to penetrate the lesion sufficiently. The improved response following occlusion was probably due to the effect of increased hydration of the stratum corneum allowing increased penetration of the drug. Although it is possible that occlusion alone would have proved therapeutic in this condition, we think that this is unlikely. The pleasing response observed in our patient to topical imiquimod cream suggests that it may be a novel treatment option worth considering for porokeratosis of Mibelli. However, more extensive investigation of efficacy and tolerability needs to be done to determine the role of imiquimod cream in the treatment of this condition.

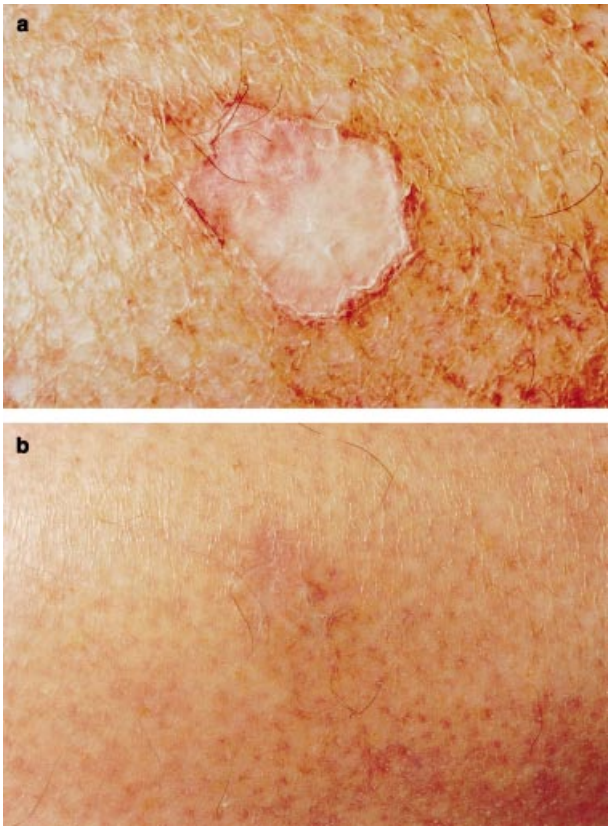

Figure 1. (a) Lesion of porokeratosis of Mibelli on the right leg; (b) resolution of the lesion after imiquimod therapy.

S. AGARWAL
J. BERTH-JONES*

Department of Dermatology, Royal Hallamshire Hospital, Sheffield S10 2JF, U.K.
**Department of Dermatology, George Eliot Hospital NHS Trust, Nuneaton, Warwickshire CV10 7DJ, U.K.*

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Paraneoplastic pemphigus triggered by Castleman's disease

SIR, Several years ago we saw a woman dying from pulmonary failure due to paraneoplastic pemphigus (PNP) triggered by Castleman's disease (CD). Being aware of this topic, we were very interested in the paper by Hsiao *et al.*,[1] the title of which promised not only a case report but also 'a review of the literature'. In the text, the authors concluded that 'a review of the English literature reveals a total of nine cases of PNP in association with CD'. Unfortunately, Hsiao *et al.* did not mention several reports that could have been found easily by a Medline search.[2–5] We wonder by which tools the authors performed their review of the literature.

Department of Dermatology and Allergology, Ludwig-Maximilians-Universität, Frauenlobstrasse 9–11, D-80337 Munich, Germany
E-mail: hans.wolff@lrz.uni-muenchen.de
H. WOLFF
G. MESSER

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Contact anaphylaxis from natural rubber latex used as an adhesive for hair extensions

SIR, A 40-year-old woman developed anaphylactic symptoms at a hair salon within minutes of contact with a natural rubber latex (NRL) adhesive used to apply hair extensions to her scalp. She first noticed palmar irritation, followed quickly by generalized pruritus, a feeling of faintness, facial oedema and difficulty in breathing. The adhesive was washed off quickly, and she was resuscitated with intramuscular adrenaline by paramedical staff en route to hospital. She received further treatment with chlorpheniramine in the accident and emergency department, and made an uneventful recovery.

The patient's hair had been chemically straightened ('relaxed') shortly before application of the NRL adhesive. This resulted in immediate irritation and soreness of the scalp. She had had this done on many previous occasions, but had never worn hair extensions. Several years previously during her work as a cardiac care staff nurse, she had noticed immediate eyelid swelling and irritation after contact with NRL examination glove powder. On changing to non-powdered gloves, her ocular symptoms cleared. She had never experienced any hand symptoms while wearing powdered NRL gloves, and was able to wear non-powdered gloves for prolonged periods after the anaphylactic episode. She had a history of mild summer hay fever but no history of fruit allergy, and had never suffered from hand dermatitis.

Skin prick tests to a low dilution (1 HEP) commercial NRL extract (Soluprick®; ALK-Abelló, Hungerford, U.K.) and a grass pollen mix were positive, and she had a class 2 RAST to latex, confirming a diagnosis of NRL hypersensitivity.

This case history highlights an unusual source of NRL exposure. Contact with items made from dipped NRL such as gloves and condoms are the most frequent cause of symptoms in allergic individuals. Medical devices such as catheters and the rubber stoppers in multidose vials are other possible sources. To the best of my knowledge, there have been no previous reports of allergic reactions from NRL adhesives, except for an isolated report of contact urticaria of the lips from an NRL adhesive in a chocolate bar wrapper.[1] The severity of her allergic reaction presumably reflects the high dose of allergen absorbed via her inflamed epidermis, as she was subsequently able to wear NRL gloves without any problems. The absence of preceding dermatological symptoms suggests that she might have been sensitized via airborne exposure to glove powder.

Healthcare workers and other professionals who regularly wear NRL gloves are at increased risk of developing NRL hypersensitivity.[2,3] Atopy and hand eczema are additional risk factors. In order to reduce the rate of sensitization to NRL and rubber chemical additives, guidelines for the quality of rubber gloves used in a healthcare setting were issued by the Medical Devices Agency in 1998.[4] These included a ban on glove powder. A decline in the rate of allergy to thiurams (rubber accelerators) in healthcare workers during the late 1990s has recently been reported.[5] Hopefully, a fall in the rate of NRL sensitization will follow suit.

Department of Dermatology, St Mary's Hospital, Paddington, London W2 1NY, U.K.
S. H. WAKELIN

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Liquid nitrogen cryotherapy of common warts: cryo-spray vs. cotton wool bud

SIR, The excellent study by Ahmed *et al.*[1] on cryotherapy for the treatment of warts caught my interest. The study showed how the methods of cotton wool bud (CWB) or a spray were equivalent for application of cryotherapy. The authors point out that CWB may be cheaper than the spray-gun method. I agree that CWBs may be cheaper in low-volume practices. Disadvantages of CWBs include the expense of the CWB being disposed of after each use (either that or replace the nitrogen but use the same CWB) and higher rate of evaporation of liquid nitrogen. I have examined dermatologists' liquid nitrogen containers and have seen 'freeze-dried skin' in the bottom of the containers, that is, the left-over matter that was picked up by the CWB while treating the patient and deposited into the liquid nitrogen container. Furthermore, the practitioners I have seen who do use the CWB method rarely replace the CWB.

I have concluded that the spray gun is more economical in a high-volume practice. The ease of use, no expense of CWBs, decreased evaporation of liquid nitrogen and therefore decreased costs all contribute to lower overall costs and better service to the patient.

Physicians who decide to use CWBs should be aware of the disadvantages. Practitioners should be aware of the possible transmission of viral particles if using the same CWB.[2] Using a spray gun has all the advantages without the disadvantages of CWBs. In a high volume practice, the upfront cost of a spray gun is worth the investment.

Department of Dermatology,
University of Oklahoma,
Oklahoma City, OK 73104, U.S.A.
E-mail: r.kuwahara@excite.com
R. T. KUWAHARA

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Liquid nitrogen cryotherapy of common warts: cryo-spray vs. cotton wool bud: reply from authors

SIR, We would like to thank Dr Kuwahara for his comments on our study. We have shown that liquid nitrogen is equally effective in treating common warts when applied either with a cryo-spray or a cotton wool bud (CWB).[1] Prior to our study, existing data relating to the response to cryotherapy were virtually all derived from the use of a CWB as the applicator.[2–4]

Cryo-spray guns have been in common use for many years. The liquid nitrogen is kept in a closed flask under pressure and has a safety-valve mechanism. They have a variety of tips and attachments to control the volume and direction of spray. We would agree with Dr Kuwahara that the cryo-spray gun is quite elegant and easy to use. Application of liquid nitrogen with a CWB is also quite easy to master, although not so elegant. When treating young children, the appearance and sound of the cryo-spray can be quite intimidating, and the CWB method may be preferred.

We did not perform a cost analysis comparing the two techniques in our study. However, the initial cost of buying a cryo-spray gun is considerable, whereas CWBs are readily available and very cheap. Most commercially available CWBs have cotton wool very tightly woven on them. In order to properly charge them with liquid nitrogen, additional cotton wool can be loosely woven on them without much effort. Five hundred CWBs cost £3 sterling (approximately $4·20). The running cost for cryotherapy is mainly the cost of liquid nitrogen. In our hospital department, liquid nitrogen is supplied to us at a cost of 35 pence (approximately 50 cents) a litre plus a fixed delivery charge at each transaction. Some general practitioners (primary care physicians) also provide a cryotherapy service for warts in their surgeries. They would perhaps undertake monthly clinics, and take their supply of liquid nitrogen from our department at a token charge of £10 (approximately $14) per quarter. Although there is perhaps less evaporation and consequently decreased loss of liquid nitrogen with a cryo-spray gun compared to an open flask when using a CWB, the overall cost of liquid nitrogen is minimal. In practice, one uses a flask or a cryo-spray load of liquid nitrogen in one session.

We agree that there is a possibility of crosscontamination with repeated dipping of the same CWB in the liquid nitrogen flask. We would therefore recommend that the CWB be dipped only once in the liquid nitrogen container and then discarded after use. Indeed, that is the practice we have in our department. The nature of residue at the bottom of a flask, which Dr Kuwahara has referred to as 'freeze-dried skin', would be interesting to elucidate. It is likely to be debris from repeated decanting and contamination.

Department of Dermatology,
University Hospitals Coventry and Warwickshire NHS Trust, Clifford Bridge Road, Coventry CV2 2DX, U.K.
I. AHMED
J. BERTH-JONES

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Topical tacrolimus and pimecrolimus are not associated with skin atrophy

SIR, The development of new topical inflammatory cytokine inhibitors such as tacrolimus (FK506, Protopic®) and pimecrolimus (SDZ ASM 981, Elidel®) will change the therapy standards in atopic dermatitis. These compounds have a similar mode of action to systemic cyclosporin, but may be used topically. Their efficacy and safety in atopic dermatitis have now been well studied[1–3] and European registration is to be expected within the next year or so. The recent publication by Queille-Roussel *et al.*[4] in which authors stated that they did not find skin atrophy in human volunteers exposed topically to pimecrolimus, raises questions about the validity of their study design.

A major drawback in the development of compounds such as tacrolimus and pimecrolimus has been that they were not effective in diseases where they were expected to make a difference. In psoriasis, one abstract shows some efficacy with topical tacrolimus, when applied under occlusion.[5] Two derivatives of its sister compound, ascomycin, were found to have similar effects in treating psoriasis topically, but again only under occlusion in Finn chamber microassays (SDZ 281–240,[6] SDZ ASM 981[7]). Without occlusion, tacrolimus was found to be ineffective as a topical therapy for psoriasis.[8] In alopecia areata, tacrolimus had no effect topically.[9]

We believe that this lack of efficacy is related to the molecular weight of these compounds. We have previously proposed the so-called 500-Da rule, which states that molecules over 500 Da will have difficulty in penetrating the corneal layer of normal human skin.[10] Tacrolimus has a molecular weight of 822 Da, pimecrolimus 811 Da. Atopic dermatitis, where a defect in the skin barrier seems to exist, provides an exception to the 500-Da rule, but cyclosporin, which has a molecular weight of 1202 Da, is ineffective topically,[11] indicating that the skin barrier dysfunction does not allow all molecules to penetrate.

The validity of the study design of Queille-Roussel *et al.* thus might be flawed, as they studied the atrophogenic potential of topical pimecrolimus in normal human skin, without occlusion (4 weeks, 6 days per week, twice daily). It might well have been that pimecrolimus did not penetrate the skin in these normal human volunteers, and could not have had any effect, let alone be atrophogenic. The fact that tolerability was excellent, and there was no reporting of immediate burning or stinging after application, indicates that there was no penetration, as burning and stinging have been mentioned in up to 40% of atopic dermatitis patients exposed to topical pimecrolimus or tacrolimus.

We do believe that pimecrolimus and tacrolimus have no atrophogenic potential, in view of their mode of action, which differs completely from that of topical corticosteroids. Furthermore, in clinical studies of atopic eczema patients, atrophy has not been observed, even after long-term use. Several years ago, Reitamo *et al.*[12] studied the atrophogenic potential of tacrolimus, also in volunteers with atopic dermatitis. In these patients, where absorption of tacrolimus might indeed have occurred, no skin atrophy could be induced.

Department of Dermatology, J.D.Bos
Academic Medical Center,
University of Amsterdam,
PO Box 22700, 1100 DE
Amsterdam, The Netherlands

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Topical tacrolimus and pimecrolimus are not associated with skin atrophy: reply from author

SIR, Professor Bos questions the validity of the study design that addresses the issue of the atrophogenic potential of pimecrolimus 1% cream (SDZ ASM 981) based on the speculative view that compounds with a molecular weight higher than 500 Da should not penetrate normal skin. Although this theory is of interest, there are few scientific data to substantiate it. Percutaneous absorption of topical drugs is a complex process and molecular weight is certainly not the only factor that determines skin penetration. Composition of the vehicle, skin site and drug concentration are among the numerous factors that can influence the percutaneous absorption of topical drugs.[1] Thus, topical cyclosporin proved to be effective in atopic dermatitis when used at 10% concentration in an oily alcohol gel.[2]

Pimecrolimus is a molecule that adequately penetrates normal human skin. Clinically relevant concentrations were found both in the dermis and in the epidermis after single topical administration to normal human skin *in vitro* (Table 1). Administration of pimecrolimus 1% cream to healthy volunteers on up to 30% of the body surface area under strict standardized conditions, thus avoiding contamination, resulted in some systemic exposure (blood concentration range 0–0·62 ng mL^{-1}). Although very low, the blood concentrations measured indicate percutaneous absorption through normal skin and are close to those recorded during treatment of adults with severe extensive atopic dermatitis (blood concentration range 0–1·4 ng mL^{-1}).[3] Absence of reporting of burning after application is definitely not an argument against penetration of a drug. Clinicians know that burning/stinging is a very common and non-specific adverse event of any type of topical application on acute atopic dermatitis lesions.

The topical treatment of psoriasis is known to be difficult and, in contrast to atopic dermatitis, few psoriasis patients can be cleared with topical agents. In a double-blind randomized controlled study in 23 patients with plaque psoriasis, pimecrolimus in an experimental 1% ointment formulation was shown to be effective without occlusion. After 21 days of twice-daily treatment, 50% reduction in severity score was achieved, as compared with 28% with the vehicle ($P < 0·05$).[4]

Overall, these data indicate that pimecrolimus 1% adequately penetrates normal as well as psoriatic human skin and that the compound appears to refute the '500-Da rule'. Consequently, the validity of our study on the atrophogenic potential of pimecrolimus is not affected.

Table 1. Distribution of pimecrolimus 1% cream in normal human skin *in vitro* (Report DMPK-R00-1030, Novartis Pharma AG, Basel, Switzerland)

Single application	10 mg cream cm^{-2}
Skin saturation (h)	0·5
Drug concentration in the epidermis including stratum corneum (μg g^{-1})	50.0
Drug concentration in the dermis (μg g^{-1})	8·1

C. QUEILLE-ROUSSEL
C. PAUL*
J-P. ORTONNE

Centre de Pharmacologie Clinique Appliquée à la Dermatologie and Service de Dermatologie, Nice University Hospital, 151 route St Antoine de Ginestière, BP 3079, Hôpital de L'Archet II, 06202 Nice cedex 3, France
**Clinical Research and Development, Novartis Pharma AG, Basel, Switzerland*
E-mail: cpcad_skinpharma@wanadoo.fr

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Recurrent angio-oedema and solitary molluscum contagiosum as presenting signs of non–Hodgkin's B-cell lymphoma

SIR, Some dermatoses that are usually benign and sporadic may occasionally occur as a consequence of internal malignancies.[1,2] As these may precede signs of the malignancy, correct interpretation of skin signs can provide an opportunity for early recognition of neoplasia and rapid initiation of adequate therapy. We report the coincident occurrence of recurrent angio-oedema and molluscum contagiosum which led to the diagnosis of non-Hodgkin's B-cell lymphoma.

A 73-year-old woman presented with recurrent swelling of the face, especially the lips, which lasted for up to 4 days. In the months prior to admission, four attacks of angio-oedema had occurred that were not affected by systemic corticosteroids or antihistamines. There was no history of hereditary angio-oedema (HAO) and she was taking no medication potentially associated with angio-oedema.

Examination showed swelling of the lower lip, but no urticaria. Additionally, a solitary skin-coloured papule of 5-mm diameter with central umbilication was noticed in the left nasolabial crease. General examination was unremarkable; in particular, there were no clinical signs of lupus

erythematosus and no lymphadenopathy. Routine laboratory values including haemoglobin (14·9 g dL^{-1}) and white blood cell count ($7{\cdot}7 \times 10^9$ L^{-1} with $5{\cdot}12 \times 10^9$ L^{-1} neutrophils and $2{\cdot}25 \times 10^9$ L^{-1} lymphocytes) were normal, and atypical peripheral lymphocytes were not detected. C1-esterase inhibitor (C1INH) concentration was reduced (6 mg dL^{-1}; normal > 21) and its functional activity was diminished (41%; normal > 70%). C4 concentration was slightly reduced, but C3 levels were normal. Antibodies against C1INH were not detectable. Total concentrations of immunoglobulins were normal, and monoclonal gammopathy, cryoglobulins and cold agglutinins were not detected. Serology for human immunodeficiency virus (HIV) was negative but she had positive test results for borreliosis [IgG positive in enzyme-linked immunosorbent assay (ELISA), immunofluorescence and western blot; IgM positive in ELISA], syphilis (treponemal haemagglutinin assay titre 1 : 640; Venereal Disease Research Laboratory test titre 1 : 64; fluorescent treponemal antibody absorption test, ELISA and western blot IgG and IgM negative), rheumatoid factor (30·6 IE; normal < 5·0) and elevated C-reactive protein (12·7 mg L^{-1}; normal < 10·1). Antinuclear antibody titre, earlier found by the patient's general practitioner to be elevated, was negative on admission. The nasolabial papule was excised and histology confirmed the clinical diagnosis of molluscum contagiosum. Chest X-ray, ultrasound of abdomen, and axillary, cervical and inguinal lymph nodes, and computed tomographic scans of neck, chest and abdomen, showed no evidence of lymphadenopathy or hepatosplenomegaly. Bone marrow biopsy revealed infiltration with a lymphoplasmocytic lymphoma, an indolent non-Hodgkin's B-cell lymphoma.

Therapy with oral chlorambucil (30 mg every 14 days) was begun. Immediately after initiation of treatment, no further attacks of angio-oedema occurred and C1INH levels increased slightly (9 mg dL^{-1}). The previously positive serological tests normalized and were interpreted as a consequence of abnormal immunoglobulin production in B-cell lymphoma; clinical signs of corresponding diseases (syphilis, lupus erythematosus, rheumatoid arthritis, borreliosis) did not develop.

Seemingly disparate disorders such as acquired angio-oedema (AAO) and molluscum contagiosum as well as false-positive serum titres for bacterial and autologous antigens may occur coincidently with malignancy or, as in our case, may lead to the diagnosis of previously unrecognized malignant disease. The dramatic improvement observed after treatment of the underlying disease clearly suggests a causal relationship between the skin and serum abnormalities and the non-Hodgkin's B-cell lymphoma in our patient.

AAO, like HAO, is characterized by a deficiency of the serine proteinase inhibitor C1INH, the only inhibitor of C1 in the complement system.[3] In AAO, loss of C1INH is a consequence of increased consumption. Paraproteins as released in lymphoproliferative diseases may have autoantibody activity and consume complement components during immune complex formation. Low levels of C1q result, which differentiate AAO from HAO. Subsequently, the complement cascade is activated, which finally leads to angio-oedema. Such mechanisms may be responsible for AAO type 1 which is most frequently associated with B-cell lymphoproliferative disorders.[4–6] Treatment of the underlying disease (by chemotherapy of the B-cell lymphoma in our patient) leads to recovery of type 1 AAO.[7] AAO type 2, a subtype not associated with underlying disease, is characterized by IgG autoantibodies binding to C1INH, which alter its structure and prevent formation of the C1s-C1INH-complex.[8] Such antibodies were not detected in our patient.

The solitary nasolabial molluscum contagiosum might have been mistaken for basal cell carcinoma, keratoacanthoma or cryptococcosis.[9] Mollusca contagiosa have been described in immunocompromised individuals, especially in those infected with HIV. Patients with lymphoma have occasionally been reported to suffer from disseminated molluscum contagiosum,[10] but a solitary lesion in these patients has not been described so far. Analogous to the situation seen in AIDS, depressed cellular immunity may predispose to molluscum contagiosum in cases of lymphoma.

Department of Dermatology, University of Würzburg, Josef-Schneider-Str. 2, 97080 Würzburg, Germany
J. ARNOLD
N. BERENS
E-B. BRÖCKER
M. GOEBELER
Correspondence: Matthias Groebeler
E-mail: goebeler-m.derma@mail.uni-wuerzburg.de

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