

EDUCATIONAL REVIEW ARTICLE

Recent Advances in Inflammatory Skin Diseases

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Abstract

Inflammatory skin diseases are frequently chronic skin conditions affecting many people at all stages of life. This article is a review intended to bring clinicians up to date with recent advances in the knowledge and management of inflammatory skin diseases, conditions that are commonly seen in general medicine and will be encountered in MRCP(UK) PACES and OSCE examinations.

Psoriasis

Psoriasis is a heterogeneous disease with a prevalence of 1.5 – 2.5%.¹ Over the last few years, much research has been focussed on the genes responsible for the pathogenesis of psoriasis. Although 19 loci have been linked with psoriasis, psoriasis susceptibility locus 1 (PSORS1) has the strongest association.² In this locus HLA-Cw-6 appears to be the important gene and other closely linked genes, such as corneodesmosin, which were previously inseparable are now thought to be associated only by linkage disequilibrium.

Animal models have provided insight into pathogenesis.³ Psoriasis is primarily a T-cell mediated condition and involves interaction of chemokines, adhesion molecules and various cytokines including Th1 cytokines.

Tumour necrosis factor alpha (TNF- α) has a very important role.³ Both T cells and TNF- α have been successfully targeted by new biological interventions (Table 1).

Table 1 - Therapies targeted at T-cells and TNF- α

T cells –	Efalizumab Alefcept
TNF- α –	Infliximab Etanercept Adalimumab

The new biologic treatments have now made the journey from the laboratory bench to dermatology clinics. Infliximab⁴, etanercept⁵ and efalizumab⁶ have been approved for treatment of moderate to severe plaque psoriasis. The National Institute for Health and Clinical Excellence (NICE) has approved etanercept and efalizumab, subject to eligibility criteria for

patients where conventional treatment is not an option either because it has failed or is contraindicated. Biologics are a welcome alternative effective treatment in psoriasis unresponsive to conventional treatments such as methotrexate, ciclosporin, etretinate and phototherapy although long-term safety data for biologic use in psoriasis is not yet available.

Infliximab is a chimeric antibody, targeting TNF- α , which is a key mediator in inflammation and has an important role in host defence and tumour growth control. A recent meta-analysis of randomised controlled trials of anti-TNF therapies, infliximab and adalimumab for rheumatoid arthritis has shown a pooled odds ratio of 3.3 for malignancies and 2.0 for serious infections.⁷ Malignancies were more common in patients who received high doses of these therapies compared with patients who received low doses; however the control group had lower than expected incidence of malignancy. The validity of this study and its conclusion has been questioned by independent clinicians.⁸ A report, based on the biologics register data by British Society for Rheumatology, looked at the rate of serious infections in anti-TNF treated rheumatoid arthritis (RA) patients and compared it with RA patients treated with disease-modifying antirheumatic drugs (DMARDs).⁹ The frequency but not the incidence for serious and soft tissue infections was increased in anti-TNF group (adjusted incidence rate ratio of 4.28).

Streptococcal upper respiratory tract infection (URTI) is one of the known causes of exacerbation of psoriasis possibly due to molecular mimicry between streptococcal M protein and keratin 17.¹⁰ Another piece of evidence by Diluvio et al¹¹ has shown an association between the two, possibly due to recruitment of skin homing T-cells in the tonsils and later their reactivation in the skin. They found identical T cell clones in skin and tonsillar tissue from patients with psoriasis, who underwent tonsillectomy with subsequent improvement in their psoriasis.

In addition to increased understanding of the genetics and pathogenesis of psoriasis, pharmacogenomics has provided tools which could help predict the efficacy and toxicity of methotrexate (MTX) in individual patients in future. Single nucleotide polymorphisms (SNPs) in Methylene tetrahydrofolate reductase gene (MTHFR) and thymidine synthase (TS) have been associated with MTX toxicity and decreased efficacy.¹² MTHFR and TS are the enzymes involved in folate metabolism and pyrimidine synthesis respectively. Hepatic fibrosis is a risk in patients receiving long term MTX. Liver function tests have been the only non-invasive way to monitor for liver fibrosis in past. The confirmation requires liver biopsies. Measurement of type III procollagen peptide assay (PIIINP) is an effective non-invasive test for ongoing hepatic fibrogenesis, however it is less reliable in monitoring patients with arthritis.¹³ Potentially, it should reduce the need for liver biopsies.

Psoriasis is also associated with increased cardiac morbidity and lipid abnormalities. In patients with severe psoriasis, the overall risk among inpatients admitted at least once for psoriasis, was increased by 50% (SMR 1.52; 95% CI: 1.44-1.60) due to cardiovascular deaths.¹⁴

A recently published population based cohort study (1987-2002) has shown that psoriasis, as an independent risk factor, is associated with an increased risk of myocardial infarction (MI) that varies with age.¹⁵ The adjusted relative risk (RR) was higher in younger psoriasis patients (RR - 1.29 and 3.10 for mild and severe psoriasis respectively) compared to older patients with psoriasis (RR - 1.08 and 1.36 respectively). This risk was still significantly greater after correcting for well known comorbidities associated with psoriasis such as smoking, alcohol consumption, obesity and hyperlipidaemia. Long-term low dose MTX treatment of psoriasis and arthritis patients has been shown to exert a significant vasculo-protective effect in form of reduced cardio-vascular morbidity. A study from the U.S. analysed the medical records of 7615 patients with psoriasis and 6707 patients with rheumatoid arthritis. Veterans, in whom, psoriasis and RA was treated with MTX, had lower relative risk of vascular disease (RR=0.73 in psoriasis and RR=0.83 in RA).¹⁶ This association was observed in patients who received a low to moderate cumulative dose of MTX. It is possible that patients who received a higher cumulative dose, had chronic and severe disease, associated with a prolonged hyper inflammatory state - hence not optimally controlled by MTX. The need for folic acid supplementation for patients on MTX is still debated. Does this reduce side effects or does it also reduce the efficacy of treatment? No fixed dose or frequency has been agreed upon but guidelines suggest supplementation of 5 mg once weekly.¹⁷ It should not be given on the day of MTX administration.

Eczema

There have also been advances in our understanding of atopic dermatitis (AD). It is a chronic inflammatory disease characterised by pruritus, eczema and cutaneous hyper reactivity. Its incidence has increased two to three fold over the last three decades.

Genetic links for AD show little overlap with those of asthma so there may be additional separate genes expressed in the skin which play an important part in the pathogenesis of AD. Some of the identified regions also overlap with those for psoriasis. That, in theory, could explain the co-occurrence of these two skin conditions in the same patient.¹⁸

An intrinsically defective skin barrier function plays a major role in disease initiation and progression. Epidermal differentiation complex on chromosome 1q21, is a locus for genes which encode proteins responsible for building and regulating barrier function.¹⁹ Genetic linkage of both psoriasis and AD to this complex suggests a role of barrier function in these diseases.

The skin barrier is important for both the water retention and preventing allergen entry into the skin. Filaggrin is the key protein involved in differentiation of epidermis and formation of the skin barrier. Recently two variants of the gene encoding for filaggrin, which predispose to AD and the dry skin frequently associated with this (Ichthyosis vulgaris), have been identified.²⁰ Filaggrin mutations are also a major risk factor for eczema-associated asthma. Irvine et al²¹ found these mutations in 50% of moderate to severe eczema and 20% of asthmatics but only if they had associated eczema. In addition, due to defects in the naturally occurring defences such as cathelicidins (LL-37) and human beta-defensin 2 (HBD-2), these patients have increased

susceptibility to various viral, fungal and bacterial infections.^{22,23} Staph aureus is particularly important and releases toxins. These act as allergens and exacerbate disease activity. Brunetti et al²⁴ tested the efficacy of ribosomal immunotherapy (Immucyral®) in 17 children with allergic and non-allergic type of eczema and found a marked improvement in the Severity Scoring of Atopic Dermatitis (SCORAD) score, an objective measurement of the severity of eczema. It is a possibility that this therapy restores the T-helper cell imbalance seen in these patients.

Twice weekly application of potent steroids can prolong remission in atopic dermatitis,²⁵ although short bursts of a potent topical steroid followed by the use of an emollient alone are as effective and safe as the long term treatment with low dose topical steroid.²⁶ Calcineurin inhibitors, pimecrolimus and tacrolimus, are useful either as an alternative to steroids or as maintenance therapy in patients unresponsive or intolerant to other agents. There is a misplaced anxiety about theoretical increased risk of skin cancers due to calcineurin inhibitors but these are not systemically absorbed and pending longer term studies there is no current evidence to support a safety concern.²⁷

Traditionally, itch is considered to be initiated in skin. An excellent review on itch has focused on the idea that brain could be the key player in pruritus.²⁸ Specific neurological pathways exist for pruritus and brain scans during experimental itch activate areas of the brain associated with pain perception. Additionally frontal areas associated with pleasure and rewards are involved which may account for habitual scratching.

A recent review of epidemiological studies looked at the association between AD and risk of cancer in these patients.²⁹ They concluded that the AD seems to have protective effect in certain cancers such as acute lymphocytic leukaemia and glioma. This could be explained by the immune surveillance hypothesis, according to which this protection is offered by an overactive immune system in AD, which destroys the abnormal cells.

Acne

Long-term antibiotics are widely used for treatment of acne. Some evidence has associated the use of antibiotics to increased incidence of infections and breast cancer. Margolis et al³⁰ looked at the incidence of URTI in 118,496 patients in the primary care research database, who had received either topical or oral antibiotics for their acne. The odds of developing an URTI in those receiving antibiotics were 2.15 compared to those who did not receive any antibiotics.

Of some concern to dermatologists prescribing long-term antibiotics, a case-control study in USA also linked antibiotics with increased incidence of incident and fatal breast cancer.³¹ This increased risk was in proportion to the increasing cumulative days of antibiotic use. The odds ratios were 1.00, 1.53, 1.68, 2.14 and 2.07 for antibiotic use of 0, 1-50, 51-100, 101-500, 501-1000 and ≥ 1001 days. The authors were unable to establish a causative relationship because other factors including the possibility of impaired immune responses in these patients could not be ruled out. A cohort study in Finland (1973-1991) also established an association between antibiotic usage and increased incidence of breast cancer.³² This posed a question on the safety of long-term antibiotics. Multiple factors could be responsible for the possible link. One possibility is that antibiotics inhibit the conversion of phytochemicals by microflora, into compounds which protect against cancer. However, another recent study involving 2.1 million females by

Friedman et al, failed to confirm a significant relationship between antibiotics and breast cancer.³³ Long-term antibiotic therapy also leads to significant problems with bacterial resistance.

Isotretinoin is now a widely used drug for treatment of severe or resistant acne. Some reports associated it with low mood or depression although the evidence is conflicting. A pilot study looked at the brain function with positron emission tomography (PET) scans in patients, who received isotretinoin and compared it with those who received antibiotics.³⁴ In isotretinoin patients, there was a decrease in brain metabolism in the orbitofrontal cortex (21% change vs. 2% change for antibiotic), an area which is associated with depression. However depression was not noticed clinically. There was a flaw in this study as subjects' scans were done at rest and not when engaged in any standardised mental activity. Subjects with headache could be found to have similar PET scan anomaly.

Lichen Planus and Hepatitis

Lichen planus (LP) is a distinctive inflammatory dermatosis likely to result from autoimmunity. Lichenoid reactions closely resembling LP can occur with certain drugs such as non-steroidal anti inflammatory drugs (NSAIDs), angiotensin converting enzyme (ACE) inhibitors, beta blockers, and methyl dopa and as part of graft versus host disease. It can affect the skin and oral mucosa. A severe form called erosive LP, affects the mucosa of the mouth and and/or genitalia. The erosive type is usually chronic and potentially premalignant.

An association has been noticed between oral lichen planus (OLP) and hepatitis C infection (HCV), especially in southern Europe and Asia. Most of the literature relates to prevalence of HCV infection in OLP rather than prevalence of OLP in HCV patients.³⁵ Incidence of HCV in LP patients remains low in UK.³⁶ It is unclear whether it is due to the diagnosis being based on clinical grounds alone rather than histo-pathological grounds. The geographical variation could partially be explained by association of HCV-related OLP with HLA class II allele HLA-DR6.³⁷ It is still to be established whether HCV is the causative organism or is present as secondary infection due to locally suppressed immune system.

Individual case reports in literature also report the occurrence of lichen planus in those children who received hepatitis B vaccine.

Blistering Diseases

Bullous pemphigoid (BP) is an autoimmune blistering condition, which occurs in older people. It has high morbidity and mortality if untreated. Different European studies have reported 19-41% mortality after one year of initiation of therapy. Venning, in 1992 reported it as 19% in UK.³⁸ We identified a high incidence in Grampian of 14 cases per million per year with a marked rise in incidence over 80 years of age.³⁹ This is likely to be an increasing problem with growing numbers of elderly patients and in Grampian 48% of patients died within two years of diagnosis. A German study showed mortality of 57% in the first year. Patients were more likely to die, if they had low serum albumin, high dose steroids (over 35 mg at discharge) and age over 80.⁴⁰ Joly et al also found that older age and low Karnofsky score were independent predictive factors for mortality.⁴¹

There is increasing evidence that it is an auto-reactive, T-cell mediated disease. BP is mediated by auto antibodies to the basement membrane zone attaching the epidermis to dermis. These auto-reactive T-cells have also been noticed in normal people. So it is hypothesised that activation of T-cells is

determined by HLA class 2 alleles.⁴²

Topical or oral steroids, depending upon the extent of disease, are the first line agents for treatment. Widespread liberal use of potent steroids is associated with lower mortality than oral steroids.^{43,44} In some patients, the disease is not fully controlled and steroid sparing agents, such as azathioprine are required. There is some evidence that high dose nicotinamide and tetracyclines are effective, usually as steroid sparing agents and in some cases on their own.^{44,45} A systematic review by the Cochrane group failed to find any significant difference for disease response when prednisolone was compared with nicotinamide and tetracyclines. Their anti-inflammatory properties are probably responsible for their efficacy.

In summary, it will be true to say that this is an exciting time for medical dermatology. Ongoing research continues to explore new possibilities in the understanding of disease pathogenesis as well as treatment.

References

1. Gelfand JM, Weinstein R, Porter SB, et al. Prevalence and treatment of psoriasis in the United Kingdom : a population-based Study. *Arch Dermatol* 2005; 141: 1537-41.
2. Elder JT. PSORS1: linking genetics and immunology. *J Invest Dermatol* 2006; 126: 1205-6.
3. Boyman O, Hefti HP, Conrad C,. Spontaneous development of psoriasis in a new animal model shows an essential role for resident T cells and tumour necrosis factor-alpha. *J Exp Med* 2004; 199: 731-6.
4. Reich K, Nestle FO, Papp K et al. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. *Lancet* 2005; 366: 1367-74.
5. Papp KA, Tying S, Lahfa M et al. A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. *Br J Dermatol* 2005; 152: 1304-12.
6. Menter A, Gordon K, Carey W et al. Efficacy and safety observed during 24 weeks of efalizumab therapy in patients with moderate to severe plaque psoriasis. *Arch Dermatol* 2005; 141: 31-8.
7. Bongartz T, Sutton AJ, Sweeting MJ, et al. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *JAMA* 2006; 295: 2275-85.
8. Dixon W, Silman A. Is there an association between anti-TNF monoclonal antibody therapy in rheumatoid arthritis and risk of malignancy and serious infection? Commentary on the meta-analysis by Bongartz et al. *Arthritis Res Ther* 2006; 8: 111.

9. Dixon WG, Watson K, Lunt M, et al. British Society for Rheumatology Biologics Register Control Centre Consortium; British Society for Rheumatology Biologics Register. Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: results from the British Society for Rheumatology Biologics Register (BSRBR). *Arthritis Rheum* 2006; 54: 2368-76.
10. Camp RDR, El-Rachkidy RG, Young HS, et al. Immunological evidence for increased reactivity to secreted *Streptococcus pyogenes* proteins in chronic plaque psoriasis:FC-13. *Br J Dermatol, Supplement* 2006; 154(supplement 1): 5.
11. Diluvio L, Vollmer S, Besgen P, et al. Identical TCR beta-chain rearrangements in streptococcal angina and skin lesions of patients with psoriasis vulgaris. *J Immunol* 2006; 176: 7104-11.
12. Campalani E, Arenas M, Marinaki AM, et al. Polymorphisms in folate, pyrimidine and purine metabolism predict clinical response to methotrexate therapy in psoriasis. *Br J Dermatol* 2006; 155: 255.
13. Chalmers RJ, Kirby B, Smith A et al. Replacement of routine liver biopsy by procollagen III aminopeptide for monitoring patients with psoriasis receiving long-term methotrexate: a multicentre audit and health economic analysis. *Br J Dermatol* 2005; 152: 444-50.
14. Mallbris L, Granath F, Hamstenn A, et al. Psoriasis is associated with lipid abnormalities at the onset of skin disease. *J Am Acad Dermatol* 2006; 54: 614-21.
15. Gelfand JM, Neimann AL, Shin DB, et al. Risk of myocardial infarction in patients with psoriasis. *JAMA* 2006; 296: 1735-41.
16. Prodanovich S, Ma F, Taylor R,. Methotrexate reduces incidence of vascular diseases in veterans with psoriasis or rheumatoid arthritis. *J Am Acad Dermatol* 2005; 52: 262-7.
17. Chakravarty K, McDonald H, Pullar T et al. British Society for Rheumatology and British Health Professionals in Rheumatology guideline for disease-modifying anti-rheumatic drug therapy (DMARD) in consultation with the British Association of Dermatologists behalf of the British Society for Rheumatology and British Health Professionals in Rheumatology Standards, Guidelines and Audit Working Group in association with the British Association of Dermatologists (BAD). *Rheumatology* 2006; epub: doi:10.1093/rheumatology/kel216a
18. Hoffjan S, Epplen JT. The genetics of atopic dermatitis: recent findings and future options. *J Mol Med* 2005; 83: 682-92.
19. Segre JA. Epidermal barrier formation and recovery in skin disorders. *J. Clin Invest* 2006; 116:1150-58.
20. Palmer CN, Irvine AD, Terron-Kwiatkowski A et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet* 2006; 38: 441-6.
21. Irvine AD, Mclean WH. Breaking the (un)sound barrier: Filaggrin is a major gene for atopic dermatitis. *J Invest Dermatol* 2006; 126: 1200-2.
22. Ong PY, Ohtake T, Brandt C et al. Endogenous antimicrobial peptides and skin infections in atopic dermatitis. *N Engl J Med* 2002; 347: 1151-60.
23. Baker BS. The role of microorganisms in atopic dermatitis. *Clin Exp Immunol* 2006; 144: 1-9.
24. Brunetti L, Francavilla R, Tesse R. Effects of oral bacterial immunotherapy in children with atopic eczema/dermatitis syndrome - a pilot study. *Biodrugs* 2005; 19: 393-99
25. Williams HC. Twice-weekly topical corticosteroid therapy may reduce atopic dermatitis relapses. *Arch Dermatol* 2004; 140: 1151-2.
26. Hoare C, Li Wan Po A, Williams HC. Systematic review of treatments for atopic eczema. *Health Technol Assess* 2000; 4(37): 1-191.
27. Ormerod A D. Topical tacrolimus and pimecrolimus and the risk of cancer: how much cause of concern? *Br J Dermatol* 2005; 153: 701-5.
28. Paus R, Schmelz M, Bíró T, et al. Frontiers in pruritus research: scratching the brain for more effective itch therapy. *J Clin Invest* 2006; 116: 1174-85.
29. Wang H, Diepgen TL. Atopic dermatitis and cancer risk. *Br J Dermatol* 2006; 154: 205-10.
30. Margolis DJ, Bowe WP, Hoffstad O, et al. Antibiotic treatment of acne may be associated with upper respiratory tract infections. *Arch Dermatol* 2005; 141: 1132-6.
31. Velicer CM, Heckbert SR, Lampe JW, et al. Antibiotic use in relation to the risk of breast cancer. *JAMA* 2004; 291: 827-35.
32. Knekt P, Adlercreutz H, Rissanen H, et al. Does antibacterial treatment for urinary tract infection contribute to the risk of breast cancer? *Br J Cancer*. 2000; 82:1107-1110.
33. Friedman GD, Oestreicher N, Chan J, et al. Antibiotics and risk of breast cancer: up to 9 years of follow-up of 2.1 million women. *Cancer Epidemiol Biomarkers Prev* 2006; 15: 2102-6.
34. Bremner JD, Fani N, Ashraf A et al. Functional brain imaging alterations in acne patients treated with isotretinoin. *Am J Psychiatry* 2005; 162: 983-91.

35. Nagao Y, Sata M. Hepatitis C virus and lichen planus. *J Gastroenterol Hepatol* 2004; 19: 1101–13.

36. Lodi G, Giuliani M, Majorana A et al. Lichen planus and hepatitis C virus: a multicentre study of patients with oral lesions and a systematic review. *Br J Dermatol* 2004; 151: 1172–81.

37. Carrozzo M, Francia Di Celle P, Gandolfo S, et al. Increased frequency of HLA-DR6 allele in Italian patients with hepatitis C virus associated oral lichen planus. *Br J Dermatol* 2001; 144: 803-8.

38. Venning VA, Wojnarowska F. Lack of predictive factors for the clinical course of bullous pemphigoid. *J Am Acad Dermatol* 1992; 26: 585-9.

39. Gudi VS, White MI, Cruickshank N et al. Annual incidence and mortality of bullous pemphigoid in the Grampian region of North-East Scotland. *Br J Dermatol* 2005; 153: 424-7.

40. Rzyany B, Partscht K, Jung M et al. Risk factors for lethal outcome in patients with bullous pemphigoid: low serum albumin level, high dosage of glucocorticosteroids, and old age. *Arch Dermatol* 2002; 138: 903-8.

41. Joly P, Benichou J, Lok C et al. Prediction of survival for patients with bullous pemphigoid: a prospective study. *Arch Dermatol* 2005; 141: 691-8.

42. Hertl M, Eming R, Veldman C. T cell control in autoimmune bullous skin disorders. *J. Clin. Invest.* 2006; 116: 1159– 66.

43. Joly P, Roujeau JC, Benichou J et al. A comparison of oral and topical corticosteroids in patients with bullous pemphigoid. *N Eng J Med* 2002; 346: 321-7.

44. Khumalo N, Kirtschig G, Middleton P, et al. Interventions for bullous pemphigoid. *Cochrane database Syst Rev* 2006; July 20(3) CD002292.

45. Fivenson DP, Breneman DL, Rosen GB, et al. Nicotinamide and tetracycline therapy of bullous pemphigoid. *Arch Dermatol* 1994; 130: 753-8.

Multiple Choice Questions

Match the stems on left side with the best answer on the right side

<p>1.</p> <p>1. Fillagrin gene mutation 2. TNF-alpha is important in pathogenesis of 3. HLACw6 4. PIII NP 5. Methyl tetrahydrofolate reductase polymorphism</p>	<p>a. Methotrexate toxicity b. Liver fibrosis c. atopic dermatitis d. PSORS 1 gene e. Psoriasis</p>
<p>2.</p> <p>1. Efalizumab 2. Etanercept 3. Staph aureus infection 4. Twice weekly potent steroids 5. High dose potent topical steroids</p>	<p>a. recommended for bullous pemphigoid b. recommended for atopic eczema c. atopic eczema d. antibody to receptor on T-cells e. anti-TNF alpha</p>
<p>3.</p> <p>1. Atopic dermatitis 2. Psoriasis 3. Bullous pemphigoid 4. Long term antibiotic therapy 5. Hepatitis C</p>	<p>a. increase risk of bacterial resistance b. decreased risk of Acute lymphocytic lymphoma c. associated with lichen planus only in certain population d. mortality 45% in two years e. increased risk of cardiovascular death</p>

Answers on page 66

Education Review Answers

Multiple choice questions on Recent advances in inflammatory skin diseases, page 34

Answers

1 1c 2e 3d 4b 5a

2 1d 2e 3c 4b 5a

3 1b 2c 3d 4a 5c