Editors' view

Drugs and the skin: psoriasis

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The skin is our largest organ, weighing over 5 kg in a 70 kg person, and provides a vital interface between the exterior and interior environments. It provides an immunologic as well as a physical barrier to invading organisms. It is often involved in systemic disease and has more than its share of organ-specific disorders including many distinctive adverse drug reactions. Because it is open to inspection, mild disease is easily detected and at one end of the spectrum there is a sometimes uncomfortable gradation from the purely cosmetic (think Botox!) to the pathological. At the severe end there are life threatening diseases such as pemphigus and toxic epidermal necrolysis. Psoriasis, one of the commoner chronic skin diseases, spans a wide range of severity and is the topic of this editors' review.

Psoriasis

Psoriasis, with a prevalence of approximately 2% of Europeans, occurs naturally exclusively in humans, although xenotransplantation of psoriatic human skin to immunodeficient mice provides an animal model. The skin and in some cases joints are affected. In moderate to severe cases >5–10% of the surface area is affected, typically on extensor surfaces (knees, elbows) scalp and nails. The commonest form, plaque psoriasis, is characterized by circumscribed red plaques which are covered by silvery scales of keratin and which readily ooze blood from abnormal vessels in the exposed base if the scale is scraped gently. Twin studies point to the importance of environmental triggers in genetically predisposed individuals. Several susceptibility loci have been identified, the strongest of which involves a mixed histocompatibility complex (MHC) allele. Factors believed to act as environmental triggers include drugs (β -adrenoceptor antagonists, non-steroidal anti-inflammatory drugs and lithium have been implicated) as well as infection (β -haemolytic streptococci, human immunodeficiency virus) and psychological stress [1].

Pathogenesis

Psoriasis is immunologically mediated (Figure 1) and is probably autoimmune in origin [2]. Innate and adaptive immune system dysregulation are both implicated, and skin microvasculature and keratinocytes are also key players. T helper type 1 (Th1) cell-derived cytokines, including interferon (IFN)- γ , and IL-2 are present in inflamed plaques but the discovery of Th17 cells has led to the realization that these are even more important than Th1 cells in the pathogenesis of psoriasis. Th17 cells differentiate under the influence of IL-1, IL-6, transforming growth factor (TGF)- β and IL-23 produced by myeloid dendritic cells [3]. They produce IL-17A and IL-22 which act on blood vessels and on keratinocytes. Psoriatic microvessels express vascular endothelial-derived growth factor and secrete increased amounts of prostaglandins and nitric oxide, influencing adhesion and transmigration of circulating leucocytes and contributing to the fragile, tortuous and leaky vessels present in psoriatic lesions. IL-17A activates keratinocytes, and keratinocyte-derived antimicrobial peptides may contribute to the initiation of disease as well as to its perpetuation via positive feedbacks (Figure 1) including its interaction with toll-like receptor (TLR)-9 on plasmacytoid dendritic cells [4].

Treatment

It is essential that treatment is commensurate with disease severity, that benefit-risk is weighed before embarking on potentially toxic (e.g. carcinogenic, immunosuppressive or liver damaging) therapy and that appropriate monitoring for toxicity is in place [5]. Therapy in mild cases consists of explanation, reassurance and emollient cream. More resistant lesions are treated with a keratolytic (e.g. salicylic acid, dithranol) applied accurately to the lesions. Topical or systemic glucocorticoids, topical vitamin D₃ analogues (e.g. calcipotriol), oral retinoids (e.g. acitretin) or psoralen with ultraviolet A light (PUVA) are used by dermatologists in

Figure 1

Some of the cells and mediators implicated in the pathogenesis of psoriasis. Antigen (top left) is recognized via a receptor such as toll-like receptor 9 (TLR-9) on an innate immune cell, e.g. a plasmacytoid dendritic cell (DC), macrophage or neutrophil, which secrete pro-inflammatory cytokines including interferon alpha (IFNα). This stimulates myeloid DC to secrete cytokines including tumour necrosis factor alpha (TNFα), IL23 and IL12. These attract and activate CD4+ve T-cells which differentiate into Th1 (in response to IL12) and Th17 (in response to IL23). Th17 cells are especially important and secrete IL22 and IL17A which stimulate angiogenesis and synergize with nitric oxide (NO) to produce abnormal leaky microvessels. These mediators also stimulate keratinocyte hyperplasia (scaly plaque is a clinical hallmark) + secretion by keratinocytes of pro-inflammatory antimicrobial peptides (e.g. cathelicidins, psoriasin) and cytokines (including IL20 and TNFα) which set up positive feedbacks and chronic disease. Mediators that are targets of effective biological drugs (Table 1) are shown in red

Table 1

Some effective biological treatments used clinically or experimentally in psoriasis

Biological treatment	Target	Licensed in UK?	Reference (if unlicensed in UK)
Etanercept	TNFα	Yes	
Infliximab	TNFα	Yes	
Adalimumab	TNFα	Yes	
Ustekinumab	IL-23	Yes	
Ixekizumab	IL-17	No	[7]
Brodalumab	IL-17	No	[8]

patients whose lesions do not improve adequately or are too extensive for exclusively topical treatment to be practicable. If such measures are ineffective, specialists will consider cytotoxic drugs (e.g. methotrexate, ciclosporin) and parenteral administration of biological drugs (Table 1). The effectiveness of biological agents that selectively block immune mediators by combining either with the mediator or with its receptor, provides evidence supporting the pathogenic role of these mediators in the disease process. Biological drugs have led to great improvements including long term remission, in many cases, even of very severe disease but potentially serious adverse effects are a

concern (some monoclonals, including alefacept and efalizumab, have been withdrawn) and the economic costs of biological drugs are high.

In the present issue of the Journal we publish a review by Rui Han and colleagues from the Psoriasis-Center, Kiel, which addresses a completely different approach to the treatment of psoriasis [6]. This is the use of oral triptolide, a small molecule (MW 483) drug which has been identified as a major active component of a Chinese medicinal herb. Triptolide has *in vitro* and *in vivo* immunosuppressant and anti-inflammatory activity and has shown promise in several immune-mediated inflammatory diseases including psoriasis. Its mechanism of action is unclear and adverse effects (including leucopenia and teratogenic effects) are by no means trivial, but it does represent a potentially important new way of addressing the substantial unmet clinical needs presented by this important disease.

REFERENCES

- 1 Griffiths C. Papulosquamous disease. In: Chapter 23.5 in Oxford Textbook of Medicine, 5th edn. eds Warrell DA, Cox TM, Firth JD. Oxford, New York: Oxford University Press, 2010; 4610–7.
- 2 Nestle FO, Kaplan DH, Barker J. Psoriasis. N Engl J Med 2009; 361: 496–509.

- 3** DiCesare A, DiMeglio P, Nestle FO. The IL-23/Th17 axis in the immunopathogenesis of psoriasis. *J Invest Dermatol* 2009; 129: 1339–50.
- 4** Lande R, Gregorio J, Facchinetti V, Chatterjee B, Wang YH, Homey B, Cao W, Wang YH, Su B, Nestle FO, Zal T, Mellman I, Schröder JM, Liu YJ, Gilliet M. Plasmacytoid dendritic cells sense self-DNA coupled with anti-microbial peptide. *Nature* 2007; 449: 564–9.
- 5** Ritter JM, Lewis LL, Mant TGK, Ferro A. Drugs and the skin. In: Chapter 51 in *A Textbook of Clinical Pharmacology and Therapeutics*, 5th edn. London: Hodder Arnold, 2008; 411–9.
- 6** Han R, Rostami-Yazdi M, Gerdes S, Mrowietz U. Triptolide in the treatment of psoriasis and other immune-mediated inflammatory diseases. *Br J Clin Pharmacol* 2012; 74: 424–36.
- 7** Leonardi C, Matheson R, Zachariae C, Cameron G, Li L, Edson-Heredia E, Braun D, Banerjee S. Anti-interleukin-17 monoclonal antibody ixekizumab in chronic plaque psoriasis. *N Engl J Med* 2012; 366: 1190–9.
- 8** Papp KA, Leonardi C, Menter A, Ortonne J-P, Krueger JG, Kricorian G, Aras G, Li J, Russell CB, Thompson EHZ, Baumbartner S. Brodalumab, an anti-interleukin-17-receptor antibody for psoriasis. *N Engl J Med* 2012; 366: 1181–9.