Clinical and Experimental Dermatology 1998; **23**: 168–172.

Pentoxifylline and skin inflammation

I.BRUYNZEEL, T.J.STOOF AND R.WILLEMZE *Department of Dermatology, Free University Hospital, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands*

Accepted for publication 5 January 1998

Summary

Cyclic nucleotide phosphodiesterase inhibitors, such as pentoxifylline, have been shown to beneficially influence a large number of inflammatory skin diseases. The biological effects of pentoxifylline on the production of proinflammatory cytokines, leukocyte–endothelial cell adhesion, chemokines and leukocyte–keratinocyte adhesion in skin inflammation are discussed.

Cyclic nucleotide phosphodiesterases play a key role in the metabolism of cAMP and cGMP. They moderate the intracellular levels of these cyclic nucleotides by increasing their rate of breakdown. It is currently known that the inactivation of cAMP and cGMP can be catalysed by not one, but rather a large number of different cyclic nucleotide phophodiesterases.[1,2] Recent data show that at least five different isoenzyme families exist and more than 20 distinct enzymes are now recognized and biological reasons for this great diversity are beginning to be unravelled, many of the isoenzymes being differently expressed and regulated in different cell types.[1,2] Inhibitors of these phosphodiesterases, which elevate intracellular cyclic nucleotide concentrations by preventing the hydrolysis of 3′,5′-cyclic nucleotides to 5′-nucleotide monophosphates, represent an important group of drugs used in a variety of diseases. Within this group, the xanthine derivatives pentoxifylline (PTX, 1-(5-oxohexyl)-3,7-dimethylxanthine), theophylline and caffeine belong to the nonselective phosphodiesterase inhibitors. They inhibit all four recognized families of cAMP phosphodiesterases as well as the fifth family of phosphodiesterases which is active on cGMP but not cAMP. More recently, more selective inhibitors of different phosphodiesterase isoenzyme families have also been identified and are currently under investigation,[2–6] but there is still little information in the literature regarding the clinical application and biological activities of these selective drugs.

The nonselective inhibitor PTX has been clinically used for decades in the treatment of a variety of microcirculatory disorders,[7] and in dermatology, a great number of skin diseases have also been shown to benefit from treatment with the drug.[8] Recently, attention has also been focused on its potential anti-inflammatory effects. For example, it was found to prevent septic shock in laboratory animals,[9] and to suppress irritant and contact hypersensitivity reactions at a dose of 600 mg q.i.d.[10,11] In a patient with ulcerating necrobiosis lipoidica, ulcers healed completely within 8 weeks at a dose of 400 mg twice daily.[12] In a patient with polyarteritis nodosa, the livedo reticularis was markedly improved and some of the nodules had resolved after 2 months at a PTX dose of 400 mg t.i.d., and after 8 months, complete remission was achieved.[13] A patient with generalized morphoea noticed softening of the skin lesions after 3 months of treatment with PTX, skin thickness measurements showing an overall reduction in affected skin thickness.[14] In a patient with intractable chronic furunculosis, new lesions ceased appearing after 2 months of treatment at a dose of 400 mg t.i.d.[15] Twenty patients with aphthous stomatitis treated with PTX (400 mg t.i.d.) were also studied monthly for 6 months. No relapses were observed during the course of treatment in 11 patients, while six experienced considerable improvement, and recurrence of the ulcers without symptomatic improvement was observed in only the remaining three patients.[16] In a preliminary, open, placebo-controlled study of 22 psoriasis patients treated with PTX (400 mg t.i.d.) for 28 days, the mean Psoriasis Area and Severity Index (PASI) decreased from 24.2 to 15.3 in the PTX group and from 20.1 to 17.3 in the placebo group.[17] Recently, the successful treatment of psoriatic skin with topically-applied PTX has been described,[18] and the successful treatment of Schamberg's disease with PTX (300 mg daily) in four patients. A significant improvement was observed within 2–3 weeks.[19] Because of this rapidly growing list of diseases which benefit from treatment with PTX, it has been suggested that the medication might be designated as the 'drug of the decade'.[20] Understanding the mechanisms underlying its beneficial effects and those of other phosphodiesterase inhibitors in such a variety of skin diseases is important in defining the optimal conditions for application of these drugs. As the great majority of the clinical investigations and *in vitro* studies have been performed

Correspondence: T.J.Stoof.

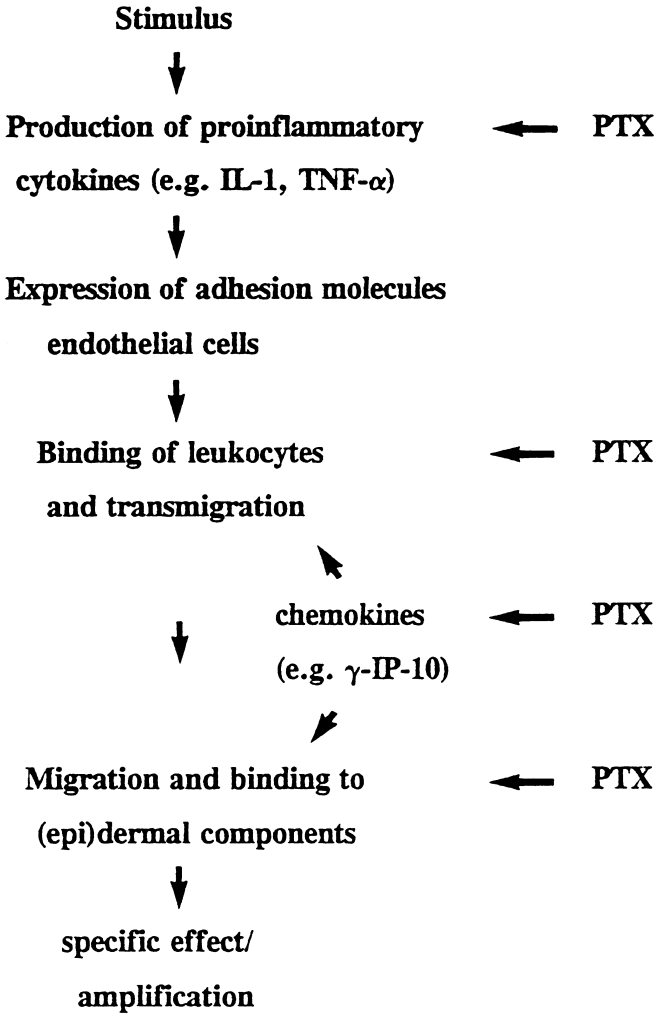

Figure 1. Four steps in process of skin inflammation: (1) stimulus induces production of pro-inflammatory cytokines by epidermal cells, which leads to expression of adhesion molecules on endothelial cells; (2) inflammatory cells adhere to vascular wall and migrate into dermis; (3) inflammatory cells travel through dermis under influence of chemotactic factors; (4) interactions take place between inflammatory cells and dermal and epidermal cells, e.g. adhesion of inflammatory cells to keratinocytes. PTX has been shown to be able to influence all four steps.

with PTX, the present paper will focus on the drug as a model for the effects of phosphodiesterase inhibitors in skin inflammation. Recent information regarding its biological effects on skin inflammation will also be discussed, and for that purpose, the development of skin inflammation is arbitrarily subdivided into four subsequent steps (Fig. 1).

PTX and pro-inflammatory cytokines

The initial event in many inflammatory skin diseases is the production of proinflammatory cytokines by epidermal and dermal cells induced by environmental challenges such as ultraviolet (UV) radiation, allergens, chemical irritants, tumour promoters and infections.[21] These stimuli can directly induce keratinocytes to produce and release pro-inflammatory cytokines, such as interleukin (IL)-1α, tumour necrosis factor (TNF)-α and IL-6.[21,22] PTX was initially described as inhibiting the liposaccharide (LPS)-induced production of TNF-α mRNA and protein by murine and human monocytes and macrophages.[11,23–36] This was shown to be modulated by an elevation of cAMP.[37,38] Recently, Neuner *et al.*[39] further demonstrated *in vivo* and *in vitro* that PTX down-regulates intercellular adhesion molecule (ICAM)-1 expression on human monocytes mediated secondary to TNF-α suppression. PTX inhibited the UVB-induced production of TNF-α by keratinocytes.[40] It was then also found to inhibit the production of interferon (IFN)-γ, IL-1, IL-6 and IL-8 by leukocytes[25,27–35] and keratinocytes (IL-1, IL-6) .[40] By inhibiting the production of pro-inflammatory cytokines by keratinocytes and leukocytes, PTX is able to prevent or diminish the first step of the inflammatory process. Furthermore, PTX has been recently shown to up-regulate the anti-inflammatory cytokine IL-10 in monocytes through cAMP elevation.[41]

PTX and leukocyte/endothelial cell adhesion

Proinflammatory cytokines such as TNF-α, IL-1 and IFN-γ have a strong inductive effect on the expression of adhesion molecules on endothelial cells, which leads to the adhesion of leukocytes to the endothelial cells and their subsequent transmigraton of leukocytes from the bloodstream into the site of inflammation.[42,43] The inhibitory effect of PTX on the production of pro-inflammatory cytokines is likely to result in a decreased upregulation of adhesion molecules on endothelial cells, and in this way interfere with the extravasation of inflammatory cells. In addition, there is mounting evidence that PTX can also directly inhibit leukocyte/endothelial cell binding. Previous studies showed that PTX inhibits the adhesion of neutrophils and monocytes to endothelial cells,[44–47] a process in which cAMP was shown to be involved.[48] More recently, it was demonstrated that PTX, at therapeutic concentrations (10^{-3}–10^{-5} M), also inhibited the adhesion of T lymphoma cells to TNF-α-stimulated mouse endothelioma cells,[49] and the adhesion of human T cells to human dermal microvascular endothelial cells (HMEC-1) .[50] This inhibition is probably the result of a change in the activation state of the adhesion molecule LFA-1 on the T lymphocytes mediated by an increase in the intracellular cAMP-level induced by PTX[50] (Fig. 2). Variable results were also found on the capacity of PTX to inhibit endothelial cell expression of ICAM-1, the ligand of lymphocyte function-associated antigen (LFA)-1, and the endothelial adhesion molecule VCAM-1. On the one hand, PTX was found to inhibit murine endothelial VCAM-1

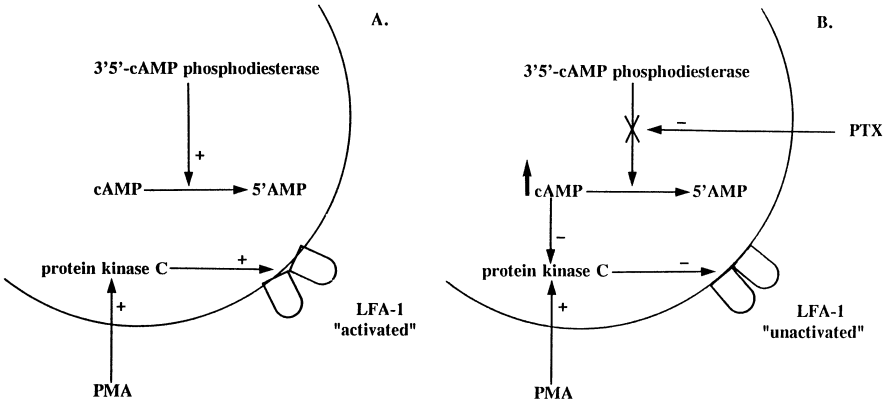

Figure 2. Effect of PTX on the activation state of the adhesion molecule LFA-1. (A) Phorbol ester phorbol myristate acetate (PMA) activates protein kinase C and thus leads to activation of LFA-1. (B) PTX inhibits intracellular phosphodiesterase, leading to elevation of cAMP which inhibits protein kinase C and prevents PMA-induced LFA-1 activation.

expression,[51] while Weiss *et al.*[49] did not find an effect of PTX on either VCAM-1 or ICAM-1 expression.

PTX and chemokines

Chemokines are members of a recently described superfamily of cytokines, subdivided into C–C (RANTES, MCP) and C–X–C (IL-8, inducible protein (IP)-10) groups, with chemotactic, cell adhesion promoting and immune response-modulating properties.[52] Chemokines can be produced by many cell types, e.g. T lymphocytes, monocytes, endothelial cells and keratinocytes.[52–54] The C–X–C chemokine IL-8, produced by keratinocytes, is considered to play an important role in the infiltration of polymorphonuclear leukocytes in the epidermis in psoriasis.[55] Similarly, keratinocyte-derived IFN-γ-induced IL-10 may be involved in the preferential influx of lymphocytes into the epidermis as observed in cutaneous T cell lymphoma.[56] Moreover, IP-10 was shown to potentiate T cell adhesion to endothelium.[57] It was shown that PTX inhibited IFN-γ-induced IP-10 (γ-IP-10) mRNA expression in cultured human keratinocytes in a dose-dependent way at pharmacological concentrations.[58] Variable results have been found on the effect of PTX on IL-8 production by peripheral blood mononuclear cells.[32–34] These studies suggest that PTX is also able to influence chemokine production, and in this way may interfere with the influx of inflammatory cells into the skin.

PTX and leukocyte/keratinocyte adhesion

After their transmigration and chemotaxis, leukocytes adhere to dermal and epidermal components like the extracellular matrix, dendritic cells and keratinocytes. Adhesion of leukocytes to other cells is an important step in skin inflammation. Previous studies have shown that T cell/keratinocyte adhesion induces the production of TNF-α, IL-6 and ICAM-1 mRNA by keratinocytes,[59] and forms an essential step in the stimulation of keratinocyte-induced T cell proliferation[60,61] and T cell mediated cytotoxicity.[62] Recently, we found that PTX, at pharmacological concentrations (10^{-3}–10^{-5} M), inhibits such adhesion of T lymphocytes to keratinocytes in a dose-dependent manner, probably also involving the above described effect of cAMP elevation on LFA-1[63] (Fig. 2). In two separate studies no inhibiting effect of PTX on the expression of the LFA-1 ligand ICAM-1 was found in cultured monolayers of keratinocytes. However, when PTX was added to human skin biopsies in short-term organ culture, the LPS- and TNF-α-induced ICAM-1 expression of keratinocytes and Langerhans cells was indeed completely inhibited;[63,64] thus far these discrepancies are unexplained.

PTX inhibits T lymphocyte/keratinocyte adhesion and thereby influences the effects of cell interactions. This can result in a reduction of cytokine release and inhibition of cell proliferation, and thus interfere with the amplification of skin inflammation. In addition, PTX may also affect T lymphocytes directly, PTX having been shown to inhibit T cell proliferation,[31] and the phytohaemagglutinin-induced production of IL-2 and IL-2 receptor expression in human peripheral blood mononuclear cells.[30,31,65]

Conclusions and perspectives

Clinical evidence has shown the potential therapeutic value of PTX in common inflammatory dermatoses, such as allergic contact hypersensitivity and psoriasis.[10,17,18] The mechanisms underlying these beneficial effects are now beginning to be understood. *In vitro* studies have shown the drug interferes with several steps of the inflammatory process and it has been shown to influence the production of proinflammatory cytokines in leukocytes and keratinocytes. Furthermore, it is able to inhibit leukocyte adhesion to endothelial cells and keratinocytes, and to decrease production of the chemokine γ-IP-10, involved in the preferential infiltration of leukocytes in several skin diseases. Together, these effects could clearly lead to a down-regulation of the inflammatory process.

In conclusion, there is accumulating evidence that

PTX, as well as related phosphodiesterase inhibitors, represent an extremely interesting group of anti-inflammatory agents with great potential in the treatment of inflammatory skin diseases; however, clinical evidence suggests that oral doses of PTX that are commonly used are not always sufficient to obtain tissue concentrations necessary for an effective anti-inflammatory effect.[66] Systemic use of higher doses of phosphodiesterase inhibitors is limited by side-effects. A highly potent and selective phosphodiesterase inhibitor, CP80,633, has recently been described by Hanifin *et al.*;[3] topical treatment of atopic dermatitis patients with it has resulted in significant clinical improvements and the reduction of inflammatory parameters. Furthermore, the successful topical application of PTX has also been described in nude mice grafted with psoriatic human skin with significant reductions in epidermal thickness.[18] Further examination of the more potent phosphodiesterase inhibitors for their anti-inflammatory effects in well-defined systems, and the development of such inhibitors that can be applied topically, is now expected to become a fruitful area of research.

References

1. Beavo JA, Reifsnyder DH. Primary sequence of cyclic nucleotide phosphodiesterase isozymes and the design of selective inhibitors. *Trends Pharmacol Sci* 1990; **11**: 150–155.
2. Nicholson CD, Challiss RAJ, Shahid M. Differential modulation of tissue function and therapeutic potential of selective inhibitors of cyclic nucleotide phophodiesterase isoenzymes. *Trends Pharmacol Sci* 1991; **12**: 19–27.
3. Hanifin JM, Chan SC, Cheng JB *et al.* Type 4 phosphodiesterase inhibitors have clinical and *in vitro* anti-inflammatory effects in atopic dermatitis. *J Invest Dermatol* 1996; **107**: 51–56.
4. Texeira MM, Rossi AG, Williams TJ, Hellewell PG. Effects of phosphodiesterase isoenzyme inhibitors on cutaneous inflammation in the guinea pig. *Br J Pharmacol* 1994; **112**: 332–340.
5. Badger AM, Olivera DL, Esser KM. Beneficial effects of the phosphodiesterase inhibitors BRL 61063, pentoxifylline, and rolipram in a murine model of endotoxin shock. *Circulatory Shock* 1994; **44**: 188–195.
6. Banner KH, Page CP. Theophylline and selective phosphodiesterase inhibitors as anti-inflammatory drugs in the treatment of bronchial asthma. *Eur Resp J* 1995; **8**: 996–1000.
7. Muller R. Pentoxifylline, a biomedical profile. *J Med* 1979; **10**: 307–329.
8. Samlaska CP, Winfield EA. Pentoxifylline. *J Am Acad Dermatol* 1994; **30**: 603–621.
9. Noel P, Nelson S, Bokulic R *et al.* Pentoxifylline inhibits lipopolysaccharide-induced serum tumor necrosis factor and mortality. *Life Sci* 1990; **47**: 1023–1029.
10. Schwarz A, Krone C, Trautinger F *et al.* Pentoxifylline suppresses irritant and contact hypersensitivity reactions. *J Invest Dermatol* 1993; **101**: 549–555.
11. Schwarz T, Schwarz A, Krone C, Luger TA. Pentoxifylline suppresses allergic patch test reactions in humans. *Arch Dermatol* 1993; **129**: 513–514.
12. Noz KC, Korstanje MJ, Vermeer BJ. Ulcerating necrobiosis lipoidica effectively treated with pentoxifylline. *Clin Exp Dermatol* 1993; **18**: 78–79.
13. Calderon MJ, Landa N, Aguirre A, Diaz-Perez JL. Successful treatment of cutaneous PAN with pentoxifylline. *Br J Dermatol* 1993; **128**: 706–707.
14. Wong SS, Holt PJA. Generalized morphoea and primary biliary cirrhosis: a rare association and improvement with oxypentifylline. *Clin Exp Dermatol* 1992; **17**: 371–373.
15. Wahba-Hahav A. Intractable chronic furunculosis: Prevention of recurrences with pentoxifylline. *Acta Derm Venereol* 1992; **72**: 461–462.
16. Pizarro A, Navarro A, Fonseca E. Treatment of recurrent aphthous stomatitis with pentoxifylline. *Br J Dermatol* 1995; **133**: 659–660.
17. Omulecki A, Broniarczyk-Dyla B, Zak-Prelich M, Choczaj-Kukula A. Is pentoxifylline effective in the treatment of psoriasis? *J Am Acad Dermatol* 1996; **34**: 714–715.
18. Gilhar A, Grossman N, Kahanovicz S *et al.* Antiproliferative effect of pentoxifylline on psoriatic and normal epidermis. *Acta Derm Venereol* 1996; **76**: 437–441.
19. Kano Y, Hirayama K, Shiohara T. Successful treatment of Schamberg's disease with pentoxifylline. *J Am Acad Dermatol* 1997; **36**: 827–830.
20. Ely H. Is pentoxifylline the drug of the decade? *J Am Acad Dermatol* 1994; **30**: 639–642.
21. Barker JNWN, Mitra RS, Griffiths CEM *et al.* Keratinocytes as initiators of inflammation. *Lancet* 1991; **337**: 211–214.
22. Stoof TJ, Boorsma DM, Nickoloff BJ. Keratinocytes and immunological cytokines. In: Leigh I, Lane B, Watt F, eds. *The Keratinocyte Handbook*. Cambridge: Cambridge University Press, 1994; 365–99.
23. Strieter RM, Remick DG, Ward PA *et al.* Cellular and molecular regulation of tumor necrosis factor-alpha production by pentoxifylline. *Biochem Biophys Res Commun* 1988; **155**: 1230–1236.
24. Han J, Thompson P, Beutler B. Dexamethasone and pentoxifylline inhibit endotoxin-induced cachectin/tumor necrosis factor synthesis at separate points in the signalling pathway. *J Exp Med* 1990; **172**: 391–394.
25. Waage A, Sorensen M, Stordal BF. Effect of pentoxifylline and HWA 138 on production of tumor necrosis and interleukin 6 from monocytes. In: Hakim J, Mandell GL, Novick WJ, eds. *Pentoxifylline and Analogues. Effects on Leukocyte Function*. Basel, Switzerland: Karger, 1990; 86–90.
26. Doherty GM, Jensen JC, Alexander HR *et al.* Pentoxifylline suppression of tumor necrosis factor gene transcription. *Surgery* 1991; **110**: 192–198.
27. Endres S, Fulle HJ, Sinha B *et al.* Cyclic nucleotides differentially regulate the synthesis of tumour necrosis factor-α and interleukin-1β by human mononuclear cells. *Immunol* 1991; **72**: 56–60.
28. Schandene L, Vandenbussche P, Crusiaux A *et al.* Differential effects of pentoxifylline on the production of tumour necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) by monocytes and T cells. *Immunol* 1992; **76**: 30–34.
29. Bienvenu J, Coulon L, Barbier M *et al.* Study of pentoxifylline induced modulation of TNFα and interleukin-6 secretion in healthy and septic patients by the use of an ex-vivo model on whole blood. *Nouv Rev Fr Hematol* 1992; **34**: S65–S67.
30. Rieneck K, Diamant M, Haahr PM *et al. In vitro* immunomodulatory effects of pentoxifylline. *Immunol Lett* 1993; **37**: 131–138.
31. Thanhauser A, Reiling N, Bohle A *et al.* Pentoxifylline: a potent inhibitor of IL-2 and IFN-γ biosynthesis and BCG-induced cytotoxicity. *Immunol* 1993; **80**: 151–156.
32. Van Leenen D, van der Poll T, Levi M *et al.* Pentoxifylline attenuates neutrophil activation in experimental endotoxemia in chimpanzees. *J Immunol* 1993; **151**: 2318–2325.
33. Neuner P, Klosner G, Schauer E *et al.* Pentoxifylline *in vivo* down-regulates the release of IL-1 beta, IL-6, IL-8 and tumour necrosis factor-alpha by human peripheral blood mononuclear cells. *Immunol* 1994; **83**: 262–267.

34. Van Furth AM, Steenwijk TM, Langermans JA, van Furth R. *In vitro* effect of dexamethasone, pentoxifylline, and anti-endotoxin monoclonal antibody on the release of proinflammatory mediators by human leukocytes stimulated with *Haemophilus influenzae* type B. *Pediatric Res* 1994; **35**: 725–728.
35. Bemelmans MH, Abramowica D, Gouma DJ *et al. In vivo* T cell activation by anti-CD3 monoclonal antibody induces soluble TNF receptor release in mice. Effects of pentoxifylline, methylprednisolone, anti-TNF, and anti-IFN-gamma antibodies. *J Immunol* 1994; **153**: 499–506.
36. Jewett A, Bonavida B. Pentoxifylline suppresses interleukin-2-mediated activation of immature human natural killer cells by inhibiting endogenous tumor necrosis factor-alpha secretion. *J Clin Immunol* 1994; **14**: 31–38.
37. Sinha B, Semmler J, Eisenhut T *et al.* Enhanced tumor necrosis factor suppression and cyclic adenosine monophosphate accumulation by combination of phosphodiesterase inhibitors and prostanoids. *Eur J Immunol* 1995; **25**: 147–153.
38. Verghese MW, McConnell RT, Strickland AB *et al.* Differential regulation of human monocyte-derived TNF alpha and IL-1 beta by type IV cAMP-phosphodiesterase (cAMP-PDE) inhibitors. *J Pharmacol Exp Therap* 1995; **272**: 1313–1320.
39. Neuner P, Klosner G, Pourmojib M *et al.* Pentoxifylline *in vivo* and *in vitro* down-regulates the expression of the intercellular adhesion molecule-1 in monocytes. *Immunology* 1997; **90**: 435–439.
40. Schwarz A, Aragane Y, Simon M *et al.* Pentoxifylline (PTX) suppresses UVB-induced cytokine release by keratinocytes. *J Invest Dermatol* 1993; **101**: 388A.
41. Platzer C, Meisel C, Vogt K *et al.* Up-regulation of monocytic IL-10 by tumor necrosis factor-alpha and cAMP elevating drugs. *Internat Immunol* 1995; **7**: 517–523.
42. Adams DH, Shaw S. Leucocyte–endothelial interactions and regulation of leucocyte migration. *Lancet* 1994; **343**: 831–836.
43. Groves RW, Allen MH, Ross EL *et al.* Tumour necrosis factor alpha is pro-inflammatory in normal human skin and modulates cutaneous adhesion molecule expression. *Br J Dermatol* 1995; **132**: 345–352.
44. Bertocchi F, Proserpio P, Lampugnani MG, Dejana E. The effect of pentoxifylline on polymorphonuclear cell adhesion to cultured endothelial cells. A preliminary report. In: Mandell GL, Novick WJ, eds. *Pentoxifylline and Leukocyte Function*. Somerville, New Jersey: Hoechst, 1988; 68–74.
45. Boogaerts MA, Malbrain S, Meeus P *et al. In vitro* modulation of normal and diseased human neutrophil function by pentoxifylline. *Blut* 1990; **61**: 60–65.
46. Wautier JL, Weill D, Setiadi H *et al.* Effect of pentoxifylline on monocyte adhesion to endothelial cells in diabetic patients. In: Hakim J, Mandell GL, Novick WJ, eds. *Pentoxifylline and Analogues. Effects on Leukocyte Function*. Basel, Switzerland: Karger 1990; 42–7.
47. Dosquet C, Weill D, Wautier JL. Molecular mechanism of blood monocyte adhesion to vascular endothelial cells. *Nouv Rev Fr Hématol* 1992; **34**: S55–S59.
48. Franzini E, Sellak H, Babin-Chevaye C *et al.* Effects of pentoxifylline on the adherence of polymorphonuclear neutrophils to oxidant-stimulated human endothelial cells: involvement of cyclic AMP. *J Cardiovasc Pharmacol* 1995; **25**: S92–S95.
49. Weiss JM, Vanscheidt W, Pilarski KA *et al.* Pentoxifylline inhibits tumor necrosis factor-α (TNFα)-induced T-lymphoma cell adhesion to endothelioma cells. *J Invest Dermatol* 1995; **104**: 824–828.
50. Bruynzeel I, van der Raaij EMH, Willemze R, Stoof TJ. Pentoxifylline inhibits human T lymphocyte adhesion to dermal endothelial cells. *Arch Dermatol Res* 1997; **289**: 189–193.
51. Bergese SD, Pelletier RP, Ohye RG *et al.* Treatment of mice with anti-CD3 mAb induces endothelial vascular cell adhesion molecule-1 expression. *Transplantation* 1994; **57**: 711–717.
52. Miller MD, Krangel MS. Biology and biochemistry of the chemokines: A family of chemotactic and inflammatory cytokines. *Crit Rev Immunol* 1992; **12**: 17–46.
53. Zachariae COC. Chemotactic cytokines and inflammation. Biological properties of the lymphocyte and monocyte chemotactic factors ELCF, MCAF and IL-8. *Acta Derm Venereol* 1991; **73**: 1–30.
54. Larsen CG, Anderson AO, Appella E *et al.* The neutrophil-activating protein (NAP-1) is also chemotactic for T lymphocytes. *Science* 1989; **243**: 1464–1466.
55. Gillitzer R, Berger R, Mielke V *et al.* Upper keratinocytes of psoriatic skin lesions express high levels of NAP-1/IL-8 mRNA in situ. *J Invest Dermatol* 1991; **97**: 73–79.
56. Sarris AH, Esgleyes-Ribot T, Crow M *et al.* Cytokine loops involving interferon-gamma and IP-10, a cytokine chemotactic for CD4+ lymphocytes: an explanation for the epidermotropism of cutaneous T-cell lymphoma? *Blood* 1995; **86**: 651–658.
57. Taub DD, Lloyd AR, Conlon K *et al.* Recombinant human interferon-inducible protein 10 is a chemoattractant for human monocytes and T lymphocytes and promotes T cell adhesion to endothelial cells. *J Exp Med* 1993; **177**: 1809–1814.
58. Stoof TJ, van de Brink EN, Willemze R, Boorsma DM. Pentoxifylline (PTX) inhibits interferon-γ (IFN-γ) induced IP-10 mRNA expression on cultured human keratinocytes (KC). *J Invest Dermatol* 1994; **103**: 442A.
59. Stoof TJ, Mitra RS, Sarma V *et al.* Keratinocyte activation following T-lymphocyte binding. *J Invest Dermatol* 1992; **98**: 92–95.
60. Simon JC, Cruz PD, Bergstresser PR *et al.* Phorbol myristate acetate-activated keratinocytes stimulate proliferation of resting peripheral blood mononuclear lymphocytes via a MHC-independent, but protein kinase C- and intercellular adhesion molecule-1-dependent, mechanism. *J Immunol* 1991; **146**: 476–484.
61. Nickoloff BJ, Mitra RS, Green J *et al.* Accessory function of keratinocytes for superantigens. Dependence on lymphocyte function-associated antigen-1/intercellular adhesion molecule–1 interaction. *J Immunol* 1993; **150**: 2148–2159.
62. Kalish RS. Non-specifically activated human peripheral blood mononuclear cells are cytotoxic for human keratinocytes *in vitro*. *J Immunol* 1989; **142**: 74–80.
63. Bruynzeel I, van der Raaij EMH, Stoof TJ, Willemze R. Pentoxifylline inhibits T cell adherence to keratinocytes. *J Invest Dermatol* 1995; **104**: 1004–1007.
64. De Fraissinette A, Berman B, Duncan MR, Lefevre L. Effects of pentoxifylline on interferon-gamma (IFN-γ) and tumour necrosis factor-alpha (TNF-α) induction of intercellular adhesion molecule-1 (ICAM-1) expression on human normal keratinocytes and Langerhans cells. *Eur J Dermatol* 1992; **2**: 265–272.
65. Rao KMK, Currie MS, McCachren SS, Cohen HJ. Pentoxifylline and other methyl xanthines inhibit interleukin-2 receptor expression in human lymphocytes. *Cell Immunol* 1991; **135**: 314–325.
66. Devault GA, Kohan DE, Nelson EW, Holman JM. The effects of oral pentoxifylline on the cytokine release syndrome during inductive OKT3. *Transplantation* 1994; **57**: 532–540.