CYCLOSPORIN A IN PSORIASIS

CYCLOSPORIN A IN PSORIASIS

PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Erasmus Universiteit van Rotterdam
op gezag van de Rector Magnificus
Prof. Dr. C.J. Rijnvos
en volgens besluit van het college van dekanen

De openbare verdediging zal plaatsvinden op
woensdag 26 juni 1991, om 13.30 uur
door

FREERK HEULE

geboren te Amsterdam

universiteits
Eburon
DRUKKERIJ
1991

Promotiecommissie:

Promotor:	Prof. Dr. Th. van Joost
Overige leden:	Prof. Dr. R. Benner
	Prof. Dr. P.R. Saxena
	Prof. Dr. M.A.D.H. Schalekamp

voor Alide
Walter, Christiaan
Peter en Roelant

The clinical studies described in this thesis were mainly performed at the Department of Dermatology, Academic Hospital Dijkzigt, Rotterdam.
The printing of this thesis was financially supported by Sandoz B.V., The Netherlands and Glaxo-Dermatology, The Netherlands.

CIP gegevens Koninklijke Bibliotheek Den Haag
Heule, Freerk
Cyclosporin A in psoriasis/Freerk Heule. - [S.I.: s.n.]. - III.
Proefschrift Rotterdam. - met lit. opg. - met samenvatting in het Nederlands
ISBN nummer 90-9004227-X
Trefwoorden: psoriasis/cyclosporin A

Contents **Page**

Chapter 1

Cyclosporin A

Summary

Introduction

Pharmacology and pharmacokinetics

Action spectrum

Known side-effects and drug interactions

References

Summary

In this introductory chapter cyclosporin A is presented with its historical background, its properties and applications. After its discovery in 1973 it was found to have immunosuppressive qualities, different from the compounds so far in use. It proved to be an (almost) perfect medicament to prevent organ graft rejection. Soon much research provided us with a boom of information on the drug and its immunopharmacological properties. During a study on its effectiveness in arthritis, it was noted to have an antipsoriatic effect in a case with psoriatic athropathy. After that experience many immune diseases were treated, also in the field of dermatology. An impressive list of some 30 diseases is shown, however, among these psoriasis seems to react the most convincingly.

Introduction

Since its introduction in the 1970's cyclosporin A (CyA) has become the drug of first choice for use in transplantation centers to prevent organ-graft rejection. The therapeutic potential of CyA was accidently discovered as a side-effect when patients with arthritis psoriatica were treated. The idea of its use as a trial drug to treat psoriasis lasted about another ten years. On the basis of theories of its mechanism of action, the in vitro studies and the numerous clinical trials (and errors) in organ transplantation which are briefly summerized in this chapter, a firm step could be made into the realm of dermatology to determine the clinical efficacy of this drug, especially in psoriasis, a disease with an acknowledged immunological background.

History

During a search for new antifungal agents, soil samples were obtained from the Hardanger Vidda, a large treeless highland plateau in the southern part of Norway in the early seventies. The fungus Tolypocladium Gams was isolated from these samples. In 1973, its most important metabolite cyclosporin A was purified, but was observed to have only mild antifungal activity [1-3]. In an additional screening program, however, Borel showed that cyclosporin A has substantial immunosuppressive properties in the absence of major

mitogenic or myelotoxic effects at pharmacological doses [4].

CyA belongs to the cyclic peptides, a group of structurally related compounds. The novel amino acid at position one and its three dimensional structure seem to be relevant for its activity [5].

Pharmacology and pharmacokinetics

The molecular formula of CyA is C62 H111 N11 012 and its molecular weight is 1202 Dalton [4]. Cyclosporin A is a white crystalline powder. It is a fermentation product of the mycelia of two strains of fungi imperfecti of the species Tolypocladium inflatum Gams and Cylindrocarpum lucidum Booth. Cyclosporin A is hydrophobic and is insoluble in aqueous solutions. It must, therefore, be dissolved in lipids before administration. The oral route is most commonly used, but it can also be administered intravenously or via intramuscular and intracutaneous administration though these routes are painful.

An effective formulation for the topical application of CyA is not yet available (see Chapter 6). In all known metabolites, the structure of CyA is preserved (Fig. 1) [6].

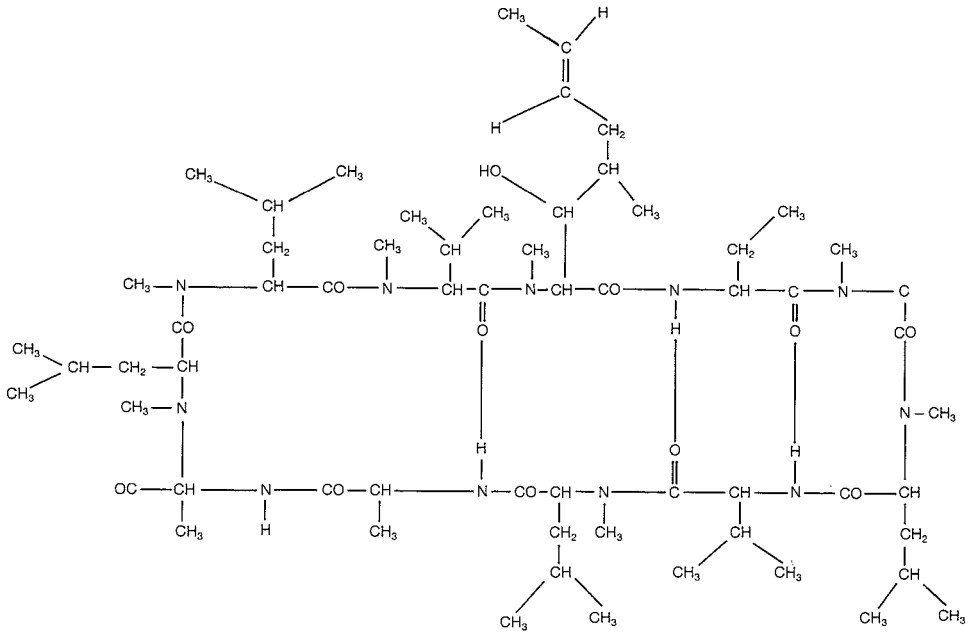


Fig. 1. Chemical structure of cyclosporin A.

Absorption

After oral ingestion, CyA is absorbed in the small intestine [7]. The amount absorbed depends on the gastrointestinal function, the transit time and the quantity of bile [8,9]. This explains the (inter)individual and daily fluctuations in CyA levels. About 98% of the drug appears in the portal circulation. The rest (2%) may then exert its first immunosuppressive effect on circulating lymphocytes via the thoracic duct [10]. On average 28% of the administered oral dose is recovered in the systemic circulation. The presence of normal serum low-density lipoprotein levels, the intake of CyA with food and prolonged therapy promote the absorption of the drug [11]. The course of the blood concentration-time curve shows a sharp peak at 1.5 to 6 hours [12]. Following intramuscular administration, the absorbtion is less and the variability is greater than after oral administration. Recently, topical application of CyA was observed to result in a transcutaneous passage of CyA to an amount that produced noticable therapeutic effect in some T cell-mediated skin disorders without general side-effects (this subject is discussed in Chapter 6).

Distribution in blood

The distribution in the central compartment depends on several factors such as absolute CyA concentration, time, temperature and hematocrit. Erythrocytes demonstrate a tenfold greater CyA binding affinity than lymphocytes [13-15]. In vitro studies showed that CyA rapidly accumulated in the cytoplasm and nucleus of mononuclear cells and granulocytes [16] and is partly bound to intracellular/cytosolic macromolecules such as cyclophilin, calmodulin and related Ca2+ dependent proteins [17-24]. Another factor that dictates the distribution in blood is the level of (high and low density) lipoproteins since CyA binds to these plasma constituents [25-26]. The binding affinity is low and CyA is readily available for distribution into the peripheral compartment.

Distribution in peripheral tissue compartments

From the plasma, free CyA passes into the interstitial fluid where it binds to lipoproteins once again. Investigations using suction blister fluid showed that whole blood and blister fluid (the analogue of interstitial fluid) concentration-time curves were parallel. This is also true for levels measured in synovial fluid from patients with rheumatoid arthritis who

were treated with CyA [27]. The concentration of CyA in blister fluid, however, is only 1/10th of that in whole blood [28-32].

The end concentration of CyA in the skin probably determines the effects in skin disorders. A recent study may illustrate this. Skin plaques of patients with psoriasis after 7 days of systemic treatment (14 mg/k/g) contain comparable concentration of CyA as the buccal mucosa in oral lichen planus patients treated with 500 mg 3 times daily using the rinse method (2.3 $\pm$ 0.3 versus 2.1 $\pm$ 0.3 ng CyA/mg tissue) [33].

After prolonged administration, other tissues usually contain high concentrations of CyA, e.g. body fat, liver, spleen, pancreas, kidney and lymph nodes [34]. Although these organs store the parent compound, the slow release of CyA does not seem to guarantee effective drug levels after cessation of treatment [35]. Saturation of the peripheral compartment, however, may result in decreased amounts of CyA being required for long-term treatment.

Metabolism and excretion

CyA is metabolized in the liver by the cytochrome-P450 system [12]. The resulting metabolites are excreted via the bile into the faeces. Enterohepatic recirculation has been reported [11]. Only 10% of biodegraded CyA is excreted into the urine [13], and because of this low level of urinary excretion, renal failure hardly alters CyA elimination [36]. A mere 1% of the unchanged drug could be detected in the faeces. These amounts may be altered by diseases or drugs which affect liver functions (see drug interactions and Table 3).

Drug clearance rates are low in elderly patients and in patients with decreased levels of serum low-density lipoprotein triglyceride and cholesterol and in patients with hepatic impairment [37].

Concentration measurements

As a consequence of the inter-individual differences in gastrointestinal absorption, hepatic biotransformation, excretion and tissue response, the measurement of CyA levels is regarded to be important for monitoring treatment and toxicity [38-45]. Currently three analytical techniques are in use. These are radioimmunoassay (RIA) [46,47], fluorescence-polarization-immunoassay (FPIA) [48] and high performance liquid chromato-

graphy (HPLC) [49]. Whole blood levels are about three to five times higher than plasma levels because CyA is adsorbed onto erythrocytes (vide supra) [36] which makes procedures for analyzing whole blood the most preferable. Parent drug only is measured using HPLC whereas, the polyclonal antiserum used in FPIA and RIA detects both CyA and its metabolites. As a result the trough levels are two to four times higher. The polyclonal antiserum to CyA for use in RIA and FPIA was recently substituted by a monoclonal antibody [50]. In clinical practice serial determinations of trough levels and doses between estimated adequate trough level-values appear an appropriate guideline [51].

Action spectrum

In vitro and animal studies

Borel and co-workers showed in their studies that CyA had a strong inhibitory effect on the proliferative response of T-cells stimulated by (allo)antigens and various mitogens. The effect on antibody synthesis, a B-lymphocyte response was minimal or absent. They concluded that T-lymphocytes were the target cells of CyA [4,52,53]. A T-cell response is triggered when antigens are expressed and recognized. This occurs when antigen presenting cells (APCs) such as macrophages, dendritic cells and Langerhans cells with class II major histocompatibility molecules on their surface present the antigen to T-helper/inducer cells. These are subsequently activated and release mediator proteins called lymphokines, which belong to the larger group of mediator proteins called cytokines. Interleukin-2 (IL-2), one of the lymphokines is a growth factor for T-cells and is responsible for clonal expansion. It is thus an autocrine growth factor for activated T-helper/inducer cells and a paracrine growth factor for cytotoxic T-cells [54].

Sensitive assays were used to study these phenomena in vitro and in vivo [reviewed in reference 55]. The production of Il-2 appears to be inhibited by CyA and consequently the proliferation of most T-cells is blocked. T-suppressor cells which generally have a low proliferative activity are not so much influenced by CyA and do not show a substantial reduction in number following CyA treatment [56-58]. CyA has no effect on T-cells that are already stimulated by IL-2. The effect on the expression of the IL-2 receptor is unknown.

Apart from the action on T-cells, CyA also affects APCs [59-61]. Macrophages are even more sensitive to CyA than T-cells regarding the inhibition of IL-2 production [62]. Similarly the drug inhibits the synthesis of gamma-interferon, the lymphokine that provides an amplification signal activating macrophages and monocytes [63].
In several disease states CyA may exert additional effects on activated cells of the involved organs. With regard to skin diseases, investigations are now also focused on keratinocytes, endothelial cells, granulocytes and fibroblasts [64-68].

The exact mechanism of immunosuppression of CyA has not yet been elucidated (Table 1). The existence of a specific CyA-receptor cyclophilin (or peptidyl-prolyl cis-trans isomerase) suggests inhibition of an early intracellular event in T-cell activation by CyA [69]. An influence on the transcription of mRNA coding for molecules like IL-2 has also been proposed [70,71] but a pretranslational interference has not been ruled out [72].

Table 1

Aspects of the action spectrum of CyA

CyA does not inhibit the recognition of an antigen by the T-cell receptor
CyA does not interfere with transmembrane signalling
CyA diffuses passively through the cell membrane
CyA is intracellularly bound to a specific receptor (cyclophilin)
CyA inhibits transcription of mRNA for many lymphokines, e.g. IL-2
CyA reduces synthesis of other activation antigens and expression of Major Histocompatibility Complex gene products

Clinical efficacy in organ transplantation and auto-immune diseases

In 1978 Calne et al demonstrated that CyA was extremely effective in preventing rejection of renal allografts [73]. After this success other organ transplants could be realized (heart, heart-lung, pancreas, bone-marrow, liver) [74]. Apart from the difficulties encountered in each case the adverse effects of CyA at relatively high doses (up to 25mg/k/d) also became apparent. The immunomodulating effect of CyA was also evaluated in a range of auto-immune diseases, some of which have dermatological aspects [75]. In a pilot study

to determine the efficacy of CyA in arthritides, it appeared that the skin lesions of a patient with psoriatic arthritis resolved [76].

Use in dermatological disorders

Besides the above mentioned diseases with an acknowledged immunological background several other diseases with a known or suspected T-lymphocyte mediated pathology were included to investigate the effects of CyA (Table 2). In this table even some conditions with questionable immunological background are listed. The exact mode of action of CyA in these conditions is not clear at present.

After the experiences of Mueller and Hermann [77], a few incidental cases reporting the clearance of psoriatic lesions during CyA treatment in transplant recipients were published [78,79].

These reports raised the question whether CyA could be of therapeutic value in treating dermatological diseases in general and psoriasis in particular.

Table 2

CyA studies in diseases with dermatological aspects other than psoriasis

Disease	References
1. Actinic reticuloid	[80]
2. Alopecia areata	[81,82] *
3. Alopecia, male pattern	[83] *
4. Atopic dermatitis	[84-90] *
5. M. Behcet	[91-94]
6. Contact dermatitis	[95-96] *
7. M. Crohn	[97-100]
8. Dermatomyositis	[101-108]
9. Eosinophilic fasciitis	[109]
10. Epidermolysis bullosa acquisita	[110-112]
11. Erythema multiforme	[113]
12. Erythema nodosum leprosum	[114]

Table 2 (continued)

CyA studies in diseases with dermatological aspects other than psoriasis

Disease	References
13. Graft versus host disease (GVHD), cutaneous	[115-117]
14. Ichthyosis	[118,119]
15. Lichen planus/-oris	[120] *
16. Lupus erythematosus variants	[121-127]
17. Mycosis fungoides (cutaneous T-cell lymphoma)	[128-132]
18. Pemphigoid, bullous	[133-135]
19. Pemphigus variants	[136-140]
20. Persistant light reaction	[141]
21. Pityriasis rubra pilaris	[142]
22. Pyoderma gangraenosum	[143-147]
23. Scleroderma	[148-150]
24. M. Sézary	[151-154]
25. M. Sjögren	[155]
26. Toxic epidermal necrolysis (TEN)	[156]
27. Ulcerative colitis	[157]

* CyA was applied topically (see references of Chapter 6).

Known side-effects and drug interactions

Known side-effects

Clinical trials in humans with high doses CyA have rendered much information on drug induced complications. Lower doses (about 5 mg/kg/d) tended to cause less side-effects but long-term regimens may evoke new problems [158].

Nephrotoxicity and hypertension [159,160], both in part related to vasoconstriction are the most frequent adverse effects. Dose reductions seemed to prevent further deterioration [161, 162]. Apart from acute toxicity and loss of (transplanted) kidneys [163], the early sign of an impact on kidney tissue is of functional nature with minimal structural changes.

After prolonged administration, however, structural changes were visible in the renal biopsies [164]. Mihatsch et al distinguished tubular toxicity (atrophy, oedema and collagen ingrowth or the appearance of giant mitochondria and microcalcification) and a chronic vasculointerstitial syndrome involving the vessels. These anatomical changes were partly irreversible [165]. The same observations were made in cases other than transplant recipients [166,167]. Explanations for these observations are only hypothetical [57,168-171].

Administration of nephrotoxic drugs before or during CyA treatment like the use of non steroid anti inflammatory drugs (NSAIDs) in rheumatoid arthritis may accelerate the effect of CyA on the kidneys [172,173,27] (see Table 3).

Hypertension is a time and dose related effect in over 20% of the patients [158]. Apart from dose reductions, antihypertensive drugs may help to control this reaction. An increase in serum lipid values and a deterioration in carbohydrate metabolism has been reported [174-177]. The role of CyA per se in bacterial, fungal and viral infections could not be substantiated as these were frequent in transplant recipients [172,176,178].

Myelotoxicity seemed to be absent [4] but lymphoproliferative disorders may evolve.

Epstein-Barr virus infections may account for increased proliferation of the B-lymphocyte pool and induce B-cell lymphomas [179-183] but a reactive B-cell amplification may also follow T-cell suppression insidiously [184-185]. Cutaneous neoplasms can be a manifestation of decreased immunosurveillance and as such, be a part of the induced immunodeficiency syndrome in an organ transplant patient [186-189].

Breast fibroadenomas in females as well as in males (gynecomastia) have been reported [163,190,191]. Hypertrichosis on the face, arms, eyebrows and back is a frequent side-effect, but mainly bothersome in women. For these effects an endocrine influence is still debated [192].

Gingival hyperplasia is comparable with the phenytoin induced reaction [163,164,191,-193]. Frequent neurological signs are tremors and burning paraesthesias including leg cramps [163,172,191]. Epileptic seizures and psychosis are seldom [191]. Depression has often been seen. Hepatotoxicity was reported with small evaluations in serum bilirubine and transaminase levels attributed to cholestasis [163,164,172,191]. Minor gastrointestinal symptoms (nausea, vomiting or diarrhoea) can occur in the first weeks of therapy and can interfere with intake and resorption of CyA [191]. These symptoms contrast with the

observations that the drug has no direct toxic effects on the structure or function of gastrointestinal mucosa.
Many of the reported side-effects are dose related and reversible.

Drug interactions
A number of drugs have been reported to interact with CyA [194]. Substances that are known to induce or inhibit the cytochrome-P450 complex in the liver either decrease or increase CyA trough levels (Table 3).
The hazardous relationship between nephrotoxic drugs and CyA treatment, has been mentioned earlier (see also Table 3).

Table 3

A summary of drugs that influence the blood trough levels of cyclosporin and increase the risk of renal dysfunction [references 194-201].

Increase CyA level	Decrease CyA level	Increase nephrotoxicity
aciclovir	barbiturates	amphotericine B iv
amphotericin B iv	carbamazepine	aminoglycosides iv/im
cimetidine	phenytoin	melphalan
prednisolone	isoniazide	NSAIDs
diltiazem	rifampicin	trimethoprim + sulphamethoxazol
doxycycline		furosemide
ketaconazole		cefuroxime
erythromycin		
nicardipine		
oral contraceptives		

Undoubtedly, the introduction of CyA is a welcome and unique addition to the range of dermatological treatment modalities. The advances in our understanding of immunological phenomena and the progress on the knowledge of the action mechanism(s) of CyA will enable us to use the drug even more effectively. In Chapters 3-8 the application of CyA in psoriasis is discussed in details.

References

1. Stähelin H. Historical background. Progr Allergy 1986; 38: 19-27.
2. Borel JF. Editorial: Cyclosporin and its future. Progr Allergy 1986; 38: 9-18.
3. White DJG. Cyclosporin A. Elsevier Biomedical Press Amsterdam 1982.
4. Borel JF, Feurer C, Gubler HU et al. Biological effects of cyclosporin A: a new antilymphocytic agent. Agents Action 1976; 6: 468-75.
5. Rich DH, Dhaon MK, Dunlap B et al. Synthesis and anti-mitogenic activities of four analogues of cyclosporin A modified in the 1 position. J Med Chem 1986; 29: 978-84.
6. Maurer G, Lemaire M. Biotransformation and distribution in blood of cyclosporine and its metabolites. Transplant Proc 1986; 18: 25-34.
7. Grevel J, Nuesch E, Abisch E et al. Pharmacokinetics of oral cyclosporin A (Sandimmun) in healthy subjects. Eur J Clin Pharmacol 1986; 31: 211-6.
8. Grevel J. Absorption of cyclosporin A after oral dosing. Transplant Proc 1986; 18: 9-15.
9. Scanlon L, Baloh R, Gridelli B et al. Determination of cyclosporine concentration in bile. Transplantation 1986; 41: 657-9.
10. Kahan BD, van Buren CT, Lin SN et al. Immunopharmacological monitoring of CyA treated recipients of cadaveric renal allografts. Transplantation 1982; 34: 36-45.
11. Kahan BD, Grevel J. Optimization of cyclosporine therapy in renal transplantation by pharmacokinetic strategy. Transplantation 1988; 46: 631-44.
12. Lemaire M, Maurer G, Wood AJ. Pharmacokinetics and metabolism. Progr Allergy 1986; 38: 93-107.
13. Wood AJ, Maurer G, Niederberger W et al. Cyclosporine: pharmacokinetics, metabolism and drug interactions. Transplant Proc 1983; 15: 2409-15.
14. Agarwal RP, McPherson RA, Threatte GA. Evidence of cyclosporine-binding protein in human erythrocytes. Transplantation 1986; 42: 627-32.
15. Niederberger W, Lemaire M, Maurer G et al. Distribution and binding of cyclosporine in blood and tissues. Transplant Proc 1983; 15: 2419-21.

16. Hess AD, Tuszynsky T, Engel P et al. Intracellular and nuclear localization of cyclosporin in peripheral blood mononuclear cells. Transplant Proc 1986; 18: 861-5.
17. Handschuhmacher RE, Harding MW, Rice J et al. Cyclophilin: a specific cytosolic binding protein for cyclosporin A. Science 1984; 226: 544-7.
18. Fabre I, Fabre G, Lena N. Kinetics of uptake and intracellular binding of cyclosporin A in Raji cells, in vitro. Biochem Pharmacol 1986; 35: 4261-6.
19. Hess AD, Colombani PM. Mechanism of action of cyclosporin: role of calmodulin, cyclophilin and other cyclosporine-binding proteins. Transplant Proc 1986; 18: 219-37.
20. Colombani PM, Bright EC, Hess AD. Cyclosporin binding to peripheral blood lymphocytes is calcium dependent. Transplant Proc 1986; 18: 866-9.
21. Hait WN, Harding MW, Handschuhmacher RE. Calmodulin, cyclophilin and cyclosporin A. Science 1986; 233: 987-9.
22. Legrue SJ, Turner R, Weisbradt N et al. Does the binding of cyclosporin to calmodulin result in immunosuppression? Science 1986; 234: 68-71.
23. Simons JW, Noga SJ, Colombani PM et al. Cyclosporine A, an in vitro calmodulin antagonist, induces nuclear lobulations in human T-cell lymphocytes and monocytes. J Cell Biol 1986; 102: 145-150.
24. Colombani PM, Robb A, Hess AD. Cyclosporin A binding to calmodulin: a possible site of action on T-lymphocytes. Science 1985; 228: 337-9.
25. Mraz W, Zink RA, Graf A et al. Distribution and transfer of cyclosporine among the various human lipoprotein classes. Transplant Proc 1983; 15: 2426-9.
26. Lemaire M, Tillement JP. Role of lipoproteins and erythrocytes in the in vitro binding and distribution of cyclosporin A in blood. J Pharm Pharmacol 1982; 34: 715-8.
27. Van Rijthoven AWAM. Cyclosporine in rheumatoid arthritis. Thesis 1990, Leiden, The Netherlands.
28. Groth S, Staberg B. Suction blisters of the skin: a compartment with physiological interstitium-like properties. Scand J Lab Invest 1984; 44: 311-6.
29. Worm AM. Exchange of macromolecules between plasma and skin interstitium in extensive skin disease. J Invest Dermatol 1981; 76: 489-92.

30. Rossing N, Worm AM. Interstitial fluid exchange of macromolecules between plasma and skin interstitium. Clin Physiol 1981; 1: 275-84.

31. Vermeer BJ, Reman FC, van Gent CM. The determination of lipids and proteins in suction blister fluid. J Invest Dermatol 1979; 73: 303-5.

32. Meinardi MMHM, van Eendenburg JP, Oosting J et al. Cyclosporin A levels in suction blister fluid of patients with psoriasis treated systemically. Br J Dermatol 1990; 122: 671-6.

33. Eisen D, Ellis CN, Duell EA et al. Effect of topical cyclosporine rinse on oral lichen planus. A double-blind analysis. N Eng J Med 1990; 323: 290-4.

34. Reid M, Gibbons S, Kwok D et al. Cyclosporine levels in human tissues of patients treated for one week to one year. Transplant Proc 1983; 15: 2434-7.

35. Maurer G. Metabolism of cyclosporine. Transplant Proc 1985; 17: 19-25.

36. Kahan BD. Individualization of cyclosporin therapy using pharmacokinetic and pharmacodynamic parameters. Transplantation 1985; 40: 457-76.

37. De Groen PC, Aksamit AJ, Rakela J et al. Central nervous system toxicity after liver transplantation: the role of cyclosporine and cholesterol. N Eng J Med 1987; 317: 861-6.

38. Klintmalm G, Sawe J, Ringden O et al. Cyclosporine plasma levels in renal transplant patients. Transplantation 1985; 39: 132-7.

39. Schran HF, Robinson WT, Abisch E et al. Bioanalytical considerations. Progr Allergy 1986; 38: 73-92.

40. Ptachcinski RJ, Burckart GJ, Venkataramanan R. Cyclosporine concentration determinations for monitoring and pharmacokinetic studies. J Clin Pharmacol 1986; 26: 358-66.

41. Holt DW, Marsden JT, Johnston A. Measurement of cyclosporine: methodological problems. Transplant Proc 1986; 18: 101-10.

42. Johnston A, Marsden JT, Holt DW. The United Kingdom cyclosporin quality assessment scheme. Ther Drug Monit 1986; 8: 200-4.

43. Atkinson K, Britton K, Biggs J. Distribution and concentration of cyclosporin in human blood. J Clin Path 1984; 37: 1167-71.

44. Smith J, Hows J, Gordon-Smith EC. In vitro stability and storage of cyclosporine in human serum and plasma. Transplant Proc 1983; 15: 2422-5.

45. Holt DW. Sandimmun monitoring, a practical guide. Sandoz 1987. Basle.
46. McBride JH, Allin RE, Ota MK et al. Technical aspects of the radioimmunoassay of cyclosporine A. Transplantation 1987; 44: 153-4.
47. Lensmeyer GL, Fields BL, Carlson IA et al. Sample pretreatment to minimize interferences from whole blood in the radioimmunoassay for cyclosporine. Transplantation 1986; 42: 372-6.
48. Keown PA. Optimizing cyclosporine therapy: Dose, levels and monitoring. Transplant Proc 1988; 20: 382-9.
49. Hosotsubo H, Takezawa J, Taenaka N et al. Determination of cyclosporin A in whole blood by HPLC using automated column switching. J Chromatogr 1986; 383: 349-55.
50. Quesniaux V, Tees R, Schreier MH. Potential of monoclonal antibodies to improve therapeutic monitoring of cyclosporine. Clin Chem 1987; 33: 32-7.
51. Versluis DJ. The use of cyclosporin A and azothioprine in clinical kidney transplantation. Thesis 1989, Rotterdam, The Netherlands.
52. Borel JF. Comparative study of in vitro and in vivo drug effects on cell mediated cytotoxicity. Immunology 1976; 31: 631-41.
53. Borel JF, Feurer C, Magnee C et al. Effects of the new anti-lymphocytic peptide cyclosporin A in animals. Immunology 1977; 32: 1017-25.
54. Mizel SB. Interleukin and T-cell activation. Immunol Rev 1982; 63: 51-72.
55. Bloemena E. Immunosuppressive mechanisms of prednisolone and cyclosporine A. Thesis, Amsterdam, The Netherlands 1989.
56. Hess AD, Tutschka PJ, Santos GW. Effect of cyclosporin A on human lymphocyte responses in vitro II. J Immunol 1981; 126: 961-8.
57. Leapman SB, Filo RS, Smith EJ et al. In vitro effects of cyclosporin A on lymphocyte subpopulations. Transplantation 1980; 30: 404-8.
58. Hess AD, Tutschka PJ. Effect of cyclosporin A on human lymphocyte responses in vitro I. J Immunol 1980; 124: 2601-8.
59. Varey AM, Champion BR, Cooke A. Cyclosporine affects the function of antigen presenting cells. Immunology 1986; 57: 111-4.
60. Knight SC, Balfour B, O'Brien J et al. Sensitivity of veiled (dendritic) cells to cyclosporine. Transplantation 1986; 41: 96-100.

61. Furue M, Katz SI. Cyclosporine A inhibits antigen-presenting and accessory cell functions of Langerhans cells. J Invest Dermatol 1987; 88: 489.

62. Paley DA, Cluff CW, Wentworth PA. Cyclosporine inhibits macrophage-mediated antigen presentation. J Immunol 1986; 136: 4348-53.

63. Yoshimura N, Kahan BD. Pharmacodynamic assessment of in vivo cyclosporine effect on interleukin-2 production by lymphocytes of kidney transplant recipients. Transplantation 1985; 40: 661-6.

64. Fisher GJ, Duell EA, Nickoloff BJ et al. Levels of cyclosporin in epidermis of treated psoriasis patients differently inhibit growth of keratinocytes cultured in serum free versus serum containing media. J Invest Dermatol 1988; 91: 142-6.

65. Umetsu DT, Katzen D, Jabara HH. Antigen presentation by human dermal fibroblasts: activation of resting T- lymphocytes. J Immunol 1986; 136: 440-5.

66. Kharazmi A, Svenson M, Nielsen H. Effect of cyclosporin A on human neutrophil and monocyte function. Scand J Immunol 1985; 21: 585-91.

67. Pigatto PD, Mozzanica N, Polenghi MM et al. Cyclosporine A inhibits polymorphonuclear leucocyte chemotaxis in vivo. Transplant Proc 1988; 20: 91-4.

68. Nickoloff BJ, Mitra RS. Direct antiproliferative effect of cyclosporin A on cultured keratinocytes and fibroblasts. Br J Dermatol 1990; 122: 693.

69. Takahaski N, Hayano T, Suzuki M. Peptidyl-prolyl cis-trans isomerase is the cyclosporin A-binding protein cyclophylin. Nature 1989; 337: 473-5.

70. Krönke M, Leonard WJ, Depper JM et al. Cyclosporin A inhibits T-cell growth factor gene expression at the level of mRNA transcription. Proc Natl Acad Sci USA 1984; 81: 5214-8.

71. Elliott JF, Lin Y, Mizel SB et al. Induction of interleukin 2 messenger RNA inhibited by cyclosporin A. Science 1984; 226: 1439-41.

72. Hodgkin PD, Hapel AJ, Johnson RM et al. Blocking of delivery of the antigen-mediated signal to the nucleus of T-cells by cyclosporine. Transplantation 1987; 43: 685-92.

73. Calne RY, White DJG, Thiru S et al. Cyclosporin A in patients receiving renal allografts from cadaver donors. Lancet 1978; ii: 1323-7.

74. Beveridge T. Clinical transplantation-overview. Progr Allergy 1986; 38: 269-92.

75. Schmitz-Schumann M. Interim report of clinical studies presented at the internatio-

nal symposium on cyclosporin in auto-immune diseases, Basle, 1985. Progr Allergy 1986; 38: 436-46.

76. Müller W, Graf U. Die Behandlung der Psoriasis arthritis mit Cyclosporin A, einem neuen Immunosuppressivum. Schweiz Med Wochenschr 1981; 111: 408.

77. Müller W, Hermann B. Cyclosporin A for psoriasis. N Engl J Med 1979; 301: 555.

78. Harper JL, Keat ACS, Staughton RCD. Cyclosporin for psoriasis. Lancet 1984; ii: 981-2.

79. Van Hooff JP, Leunissen KML, van der Staak W. Cyclosporin for psoriasis. Lancet 1985; i: 335.

80. Thestrup-Pedersen K, Zachariae C, Kaltoft K et al. Development of cutaneous pseudolymphoma following cyclosporin therapy of actinic reticuloid. Dermatologica (Basel) 1988; 177: 376-81.

81. Gebhart W, Schmidt JB, Schemper M et al. Cyclosporin-A-induced hairgrowth in human renal allograft recipients and alopecia areata. Arch Dermatol Res 1986; 278: 238-40.

82. Gupta AK, Ellis CN, Tellner DC et al. Treatment of severe alopecia areata with oral cyclosporine. Clin Res 1988; 36: 652a.

83. Picascia DD, Roeningk HH. The effects of oral and topical cyclosporine in male pattern alopecia. Transplant Proc 1988; 20: 109-11.

84. Van Joost Th, Stolz E, Heule F. Efficacy of low-dose cyclosporine in severe atopic disease. Arch Dermatol 1987; 123: 166-7.

85. De Prost Y, Bodemer C, Teillac D. Double-blind randomized placebo-controlled trial of local cyclosporine in atopic dermatitis. Arch Dermatol 1989; 125: 570.

86. Logan RA, Camp RDR. Severe atopic eczema: response to oral cyclosporine A. J Roy Soc Med 1988; 81: 417-8.

87. Taylor RS, Baadsgaard O, Headington JT et al. Epidermal activation of autoreactive T cells in atopic dermatitis: response to cyclosporine A. Clin Res 1988; 36: 699a.

88. Gold MH, Picascia DD, Roeningk HH. Treatment-resistant atopic dermatitis controlled with cyclosporin A. Int J Dermatol 1989; 28: 481-2.

89. De Prost Y. Traitement de la dermatite atopique par la cyclosporine. Ann Derm

Vénéréol 1989; 116: 79-80.

90. Motley RJ, Whittaker JA, Holt PJA. Resolution of atopic dermatitis in a patient treated with cyclosporin. Clin Exp Dermatol 1989; 14: 243-4.

91. French-Constant C, Wolman R, Geraint JD. Cyclosporin in Behcet's disease. Lancet 1983; i: 1955.

92. Sanders MD, Geraint JD, Graham E et al. Cyclosporin in Behcet's disease. Lancet 1983; ii: 454-5.

93. Nussenblatt RB, Palestine AG, Chan C et al. Effectiveness of cyclosporin therapy for Behcet's disease. Arthritis Rheum 1985; 28: 671-9.

94. Müftuoglu AU, Pazaru H, Yurdakul S et al. Short-term cyclosporin A treatment of Behcet's disease. Br J Ophthal 1987; 71: 387-90.

95. Rullan PD, Barr RJ, Cole GW. The effect of cyclosporine on murine allergic contact dermatitis. Arch Dermatol 1984; 120: 1179-83.

96. Mijachi Y. The effect of cyclosporin A on murine contact photosensitivity. Photodermatol 1986; 3: 353-5.

97. Marbet UA, Gyr K, Stalder GA. Cyclosporin A beim Morbus Crohn: erste Erfahrungen. Schweiz Med Wochenschr 1986; 116: 962-3.

98. Allison MC, Pounder RE. Cyclosporine for Crohn's disease. Lancet 1984; i: 902-3.

99. Bianchi PA, Mondelli M. Quarto di Palo F et al. Cyclosporine for Crohn's disease. Lancet 1984; i: 1242.

100. Brynskov J, Freund L, Rasmussen SN. A placebo-controlled, double-blind randomized trial of cyclosporine. Therapy in active Crohn's disease. N Eng J Med 1989; 321: 845-51.

101. Ejstrup L. Severe dermatomyositis treated with cyclosporin A. Ann Rheum Dis 1986; 45: 612-3.

102. Ganser G, Spieker C, Raidt H et al. Cyclosporin A bei Dermatomyositis. Schweiz Rundschau Med Praxis 1984; 73: 741-3.

103. Zabel G, Leimanstoll G, Gross WL. Cyclosporin for acute dermatomyositis. Lancet 1984; i: 343.

104. Gruhn WB, Diaz-Buxo JA. Cyclosporine treatment of steroid-resistant interstitial pneumonitis associated with dermatomyositis/polymyositis. J Rheumatol 1987; 14:

1045-7.

105. Levi S. Hodgson HJF. Cyclosporin for dermatomyositis ? Ann Rheum Dis 1989; 48: 85-6.

106. Girardin E, Dayer JM, Paunier L. Cyclosporine for juvenile dermatomyositis. J Pediat 1988; 112: 165-6.

107. Heckmatt J, Hasson N, Saunders C et al. Cyclosporin in juvenile dermatomyositis. Lancet 1989; i: 1063-6.

108. Reinert P, Hamberger C, Rahimy MC et al. Interêt de la cyclosporine A dans la dermatomyosite de l'enfant. Arch Franc Pediat 1988; 45: 201-3.

109. Debusscher L, Bitar N, De Mauberge J et al. Eosinophilic fasciitis and severe aplastic anemia: favorable response to either antithymocyte globulin or cyclosporin A in blood and skin disorders. Transplant Proc 1988; 20: 310-3.

110. Connolly SM, Sander HM. Successful treatment of epidermolysis bullosa acquisita with cyclosporine: a case report. J Am Acad Dermatol 1987; 16: 890.

111. Crow LL, Finkle JP, Gammon WR et al. Clearing of epidermolysis bullosa acquisita with cyclosporine. J Am Acad Dermatol 1988; 19: 937-42.

112. Zachariae H. Cyclosporine A in epidermolysis bullosa acquisita. Am Acad Dermatol 1987; 17: 1058-9.

113. McDonald CJ. Cyclosporine clears bullous erythema multiforme. Skin and Allergy News, February 1988; p 4.

114. Miller RA, Shen JY, Rea TH et al. Treatment of chronic erythema nodosum leprosum with cyclosporine A produces clinical and immunohistologic remission. Int J Leprosy 1987; 55: 441-9.

115. Palon J, Martin E, Mascaro DM et al. Cyclosporin A and graft-vs-host disease. Am J Dermatopathol 1986; 8: 90-1.

116. Harper JL, Kendra JR, Desai S et al. Dermatological aspects of cyclosporin A for prophylaxis of graft-versus-host disease. Br J Dermatol 1984; 110: 469-74.

117. Read D, Pierard GE, De la Brassine M et al. Traitement de la réaction cutanée aïgue du greffon contre l'hôte par cyclosporine et PUVA. Ann Derm Vénéréol 1988; 115: 427-31.

118. Velthuis PJ, Jesserun RFM. Improvement of ichthyosis by cyclosporin. Lancet 1985; i: 335.

119. Ho VC, Gupta AK, Ellis CN et al. Cyclosporine in lamellar ichthyosis. Arch Dermatol 1989; 125: 511-4.

120. Ho VC, Gupta AK, Ellis CN et al. Treatment of severe lichen planus with cyclosporine. J Am Acad Dermatol 1990; 22: 64-8.

121. Isenberg DA, Snaith MI, Morrow WJW et al. Cyclosporin A for the treatment of systemic lupus erythematosus. Int J Immunopharmacol 1981; 3: 163-9.

122. Le Francois N, Deleix P, Laville P et al. Treatment of systemic lupus with cyclosporin A: a patient with a one year follow-up. Kidney Int 1984; 26: 225.

123. Miescher DA, Beris PH. Ciclosporin in der Behandlung der Lupus erythematodes disseminatus (LED) und der rheumatoiden Arthritis (RA). Internist 1985; 26: 575-7.

124. Feutren G, Quérin S, Tron F et al. The effects of cyclosporine in patients with systemic lupus. Transplant Proc 1986; 18: 643-4.

125. Heule F, van Joost Th, Beukers R. Cyclosporin in the treatment of lupus erythematosus. Arch Dermatol 1986; 122: 973-4.

126. Miescher PA, Favre H, Chatelanat F et al. Combined steroid-cyclosporin treatment for chronic autoimmune diseases. Clinical results and assessment of nephrotoxicity by renal biopsy. Klin Wochenschr 1987; 65: 727-36.

127. Russel AS, Bretscher PA. Immunosuppressive therapy in systemic lupus erythematosus. J Rheumatol 1987; 14: 194-8.

128. Maddox A, Kahan BD, Tucker S et al. Remission in skin infiltrate of a patient with mycosis fungoides treated with cyclosporine. J Am Acad Dermatol 1985; 12: 952-6.

129. Moreland AA, Robertson DB, Heffner LT. Treatment of cutaneous T cell lymphoma with cyclosporin A. J Am Acad Dermatol 1985; 12: 886-7.

130. Jensen JR, Thestrup-Pedersen K, Zachariae H et al. Cyclosporin A therapy for mycosis fungoides. Arch Dermatol 1987; 123: 160-3.

131. Thomsen K, Wantzin GL. Extracutaneous spreading with fatal outcome of mycosis fungoides in a patient treated with ciclosporin A: a word of caution. Dermatologica (Basel) 1987; 174: 236-8.

132. Kreis W, Budman DR, Shapiro PE. Cyclosporin A (cyclosporine) in the treatment of cutaneous T cell lymphoma (mycosis fungoides). J Am Acad Dermatol 1988;

18: 1138-40.

133. Thivolet J, Barthelemy H, Rigot-Muller G et al. Effects of cyclosporin on bullous pemphigoid and pemphigus. Lancet 1985; i: 334-5.

134. Barthelemy H, Thivolet J, Cambazard F et al. La cyclosporine dans le traitement de la pemphigoide bulleuze: étude préliminaire. Ann Dermatol Vénéréol 1986; 113: 309-13.

135. Cunliffe WJ. Bullous pemphigoid and response to cyclosporin. Br J Dermatol 1987; 117, suppl. 32: 113-4.

136. Steiner A, Diem E. Pemphigus vulgaris- maligner Verlauf. Hautarzt 1986; 37: 499-502.

137. Balda BR, Rosenzweig D. Cyclosporin A in der Behandlung von Pemphigus foliaceus und Pemphigus erythematosus. Hautarzt 1986; 37: 454-7.

138. Cunliffe WJ. Pemphigus foliaceus and response to cyclosporin. Br J Dermatol 1987; 117, suppl. 32: 114-6.

139. Barthelemy H, Frappaz A, Cambazard F et al. Treatment of nine cases of pemphigus vulgaris with cyclosporine. J Am Acad Dermatol 1988; 18: 1262-6.

140. Alijotas J, Pedragosa R, Bosch J et al. Prolonged remission after cyclosporine therapy in pemphigus vulgaris: report of two young siblings. J Am Acad Dermatol 1990; 23: 701-3.

141. Duchet P, Schwarz T, Oppolzer G et al. Persistant light reaction: successful treatment with cyclosporin A. Acta Derm Venereol (Stockh) 1988; 68: 176-8.

142. Meyer P, van Voorst-Vader PC. Lack of effect of cyclosporin A in pityriasis rubra pilaris. Acta Derm Venereol (Stockh) 1989; 69: 272.

143. Curley RK, MacFarlane AW, Vickers CFH. Pyoderma gangrenosum treated with cyclosporin A. Br J Dermatol 1985; 113: 601-4.

144. Penmetcha M, Navaratnam AE. Pyoderma gangrenosum: response to cyclosporin A. Int J Dermatol 1988; 27: 253.

145. Shelley ED, Shelley WB. Cyclosporine therapy for pyoderma gangrenosum associated with sclerosing cholangitis and ulcerative colitis. J Am Acad Dermatol 1988; 18: 1084-8.

146. Magid ML, Gold MH. Treatment of recalcitrant pyoderma gangrenosum with cyclosporine. J Am Acad Dermatol 1989; 20: 239-94.

147. Elgart G, Larson K, Stover P et al. Effective treatment of pyoderma gangrenosum with cyclosporin: a report of five cases. Clin Res 1989; 37: 749a.

148. Appelboom T, Itzkowit D. Cyclosporine in successful control of rapidly progressive scleroderma. A case report. Am J Med 1987; 82: 866-7.

149. Francès C, Branchet MC, Boisnic S et al. Etude de collagène cutané de malades sclérodermiques avant et après traitement par la ciclosporine (CsA). Ann Derm Vénéréol 1987; 114: 470.

150. Francès C, Branchet MC, Bletry O et al. Skin collagen from scleroderma patients before and after cyclosporin A treatment. Clin Exp Dermatol 1988; 13: 1-3.

151. Catterall MD, Addis BJ, Smith JL et al. Sézary syndrome: Transformation to a high grade T cell lymphoma after treatment with cyclosporin. Clin Exp Dermatol 1983; 8: 159-69.

152. Puttick L, Pollock A, Fairburn E. Treatment of Sézary syndrome with cyclosporin A. J R Soc Med 1983; 76: 1063-5.

153. Töttermann TH, Scheynius A, Killander A et al. Treatment of therapy resistant Sézary syndrome with cyclosporin A: suppression of pruritis, leukemic T cell activation markers and tumour mass. Scand J Hematol 1985; 34: 196-203.

154. Ramon D, Betlloch I, Jiminez A et al. Remission of Sézary's syndrome with cyclosporin A. Mild capillary leak syndrome as an unusual side effect. Acta Dermatovenerol 1986; 66: 80-2.

155. Drosos AA, Skopouli FN, Costopulos JS et al. Cyclosporin A (CsA) in primary Sjögren's syndrome: a double blind study. Ann Rheum Dis 1986; 45: 732-5.

156. Renfro L, Grant-Kels JM, Daman AL. Drug-induced toxic epidermal necrolysis treated with cyclosporin. Int J Dermatol 1989; 28: 441-4.

157. Gupta S, Keshavarzian A, Hodgson HJF. Cyclosporin in ulcerative colitis. Lancet 1984; ii: 1277-8.

158. De Rie MA, Meinardi MMHM, Bos JD. Analysis of side-effects of medium-and low-dose cyclosporin maintenance therapy in psoriasis. Br J Dermatol 1990; 23: 347-53.

159. Calne RY, White DJG, Thiru S et al. Cyclosporin A in patients receiving renal allografts from cadaver donors. Lancet 1978; ii: 1323-7.

160. Calne RY, Rolles K, White DJG et al. Cyclosporin A initially as the only immu-

nosuppressant in 34 recipients of cadaveric organs: 32 kidneys, 2 pancreases and 2 livers. Lancet 1979; ii: 1033-6.

161. Johnson RWG, Wise MH, Bakran A et al. A four-year prospective study of cyclosporine in cadaver renal transplantation. Transplant Proc 1985; 17: 1197-200.

162. Klintmalm G, Bohman SO, Sundelin B et al. Interstitial fibrosis in renal allografts after 12-40 months of cyclosporin treatment. Beneficial effects of lower doses early after transplantation. Lancet 1984; ii: 950-4.

163. Ferguson RM, Rynasiewicz JJ, Sutherland DER et al. Cyclosporin A in renal transplantation: A prospective randomized trial. Surgery 1982; 92: 175-82.

164. Thiel G, Harder F, Lörtscher R et al. Cyclosporin A used alone or in combination with low-dose steroids in cadaveric renal transplantation. Klin Wochenschr 1983; 61: 991-1000.

165. Mihatsch MJ, Thiel G, Ryffel B. Histopathology of cyclosporine nephrotoxicity. Transplant Proc 1988; 20, suppl 3: 759-71.

166. Palestine AG, Austin HA, Balow JE et al. Renal histopathologic alterations in patients treated with cyclosporine for uveitis. N Eng J Med 1986; 314: 1293-8.

167. Mihatsch MJ, Thiel G, Ryffel B. Morphology of ciclosporin-nephropathy in autoimmune disease. In: Ciclosporin (Sandimmune^{R}) in psoriasis. Van Joost Th, Heule F, Bos JD. Eds. Actua Sandoz 1988; 13: 137-47. Samson Stafleu, Alphen a/d Rijn, The Netherlands.

168. Sullivan BA, Hak LJ, Finn WF. Cyclosporine nephrotoxicity: studies in laboratory animals. Transplant Proc 1985; 17, suppl 1: 145-54.

169. Bennet WM. Basic mechanisms and pathophysiology of cyclosporine nephrotoxicity. Transplant Proc 1985; 17, suppl 1: 297-302.

170. Neild GH, Reuben R, Hartley RB et al. Glomerular thrombi in renal allografts associated with cyclosporin treatment. J Clin Pathol 1985; 38: 253-8.

171. Neild GH, Rocchi G, Imberti L et al. Effect of cyclosporine on prostacyclin synthesis by vascular tissue in rabbits. Transplant Proc 1983; 15: 2398-400.

172. The Canadian Multicentre Transplant Study Group. A randomized clinical trial of cyclosporine in cadaveric renal transplantation. N Eng J Med 1983; 309: 809-15.

173. Termeer A, Hoitsma AJ, Koene RAP. Severe nephrotoxicity caused by the combined use of gentamicin and cyclosporine in renal allograft recipients. Trans-

plantation 1986; 42: 220-1.

174. Harris KPG, Russel GI, Parvin SD et al. Alterations in lipid and carbohydrate metabolism attributable to cyclosporin A in renal transplant recipients. Br Med J 1986; 292: 16.

175. Jutte NHPM, Heyse P, Bruining GJ et al. Effects of cyclosporine A on glucose-induced insulin secretion by isolated human islets of Langerhans. Transplant Proc 1987; 19: 4152.

176. Sutherland DER, Payne WD, Fryd DS et al. Comparison of cyclosporine and azothioprine for immunosuppression in diabetic and nondiabetic renal allograft recipients. Transplant Proc 1985; 17: 1204-11.

177. Draznin B, Metz SA, Sussman KE et al. Cyclosporin-induced inhibition of insulin release. Possible role of low voltage dependent calcium transport channels. Biochem Pharmacol 1988; 37: 3941-5.

178. Bencini PL, Montagnino G, Crosti C et al. Acne in a kidney transplant patient treated with cyclosporin A. Br J Dermatol 1986; 114: 396-7.

179. Graham Bird A, McLachlan SM, Britton S. Cyclosporin A promotes spontaneous outgrowth in vitro of Epstein Barr virus-induced B-cell lines. Nature 1981; 289: 300-1.

180. Nagington J, Gray J. Cyclosporin A immunosuppression, Epstein-Barr antibody and lymphoma. Lancet 1980; i: 536-7.

181. Crawford DH, Thomas JA, Janossi G et al. Epstein-Barr virus nuclear antigen positive lymphoma after cyclosporin A treatment in patients with renal allograft. Lancet 1980; i: 1355-6.

182. Thiru S, Calne RY, Nagington J. Lymphoma in renal allograft patients treated with cyclosporin A as one of the immunosuppressive agents. Transplant Proc 1981; 13: 359-64.

183. West JC, Kelley SE, Pezzi CM. Cyclosporin-induced lymphomas; controversies in diagnosis and treatment. Transplant Proc 1981; 18: 1450-4.

184. Beveridge T, Krupp P, McKibbon C. Lymphomas and lymphoproliferative lesions under cyclosporin therapy. Lancet 1984; i: 788.

185. Starzel T, Porter K, Inatsuki S et al. Reversibility of lymphomas and lymphoproliferative lesions developing under cyclosporine-steroid therapy. Lancet 1984; i:

583-7.

186. Penn I. Cancers following cyclosporine therapy. Transplantation 1987; 43: 32-5.

187. Bencini PL, Montagnino G, Scala F et al. Cutaneous lesions in 67 cyclosporin-treated renal transplant recipients. Dermatologica 1986; 172: 24-30.

188. Thompson JP, Allen R, Morris PJ et al. Skin cancer in renal transplant patients treated with cyclosporine. Lancet 1985; i: 158-9.

189. Mérot Y, Miescher PA, Balsiger F et al. Cutaneous malignant melanomas occuring under cyclosporin A therapy: a report of two cases. Br J Dermatol 1990; 123: 237-9.

190. Calne RY, White DJG, Evans DB et al. Cyclosporin A in cadaveric organ transplantation. Br Med J 1981; 282: 934-6.

191. European Multicentre Trial Group. Cyclosporine in cadaveric renal transplantation: one-year follow-up of a multicentre trial. Lancet 1983; ii: 986-9.

192. Raifer J, Sikka CS, Lemmi C et al. Cyclosporine inhibits testosterone biosynthesis in the rat testis. Endocrinology 1987; 121: 586-9.

193. Tydesley WR, Rotter E. Gingival hyperplasia induced by cyclosporine A. Br Dnt J 1984; 157: 305-6.

194. Van Joost Th, Heule F, Wenting GJ. De behandeling van psoriasis met ciclosporine. Geneesmiddelenbulletin 1990; 24: 10 (ISSN 0304-4629).

195. Keown PA, Laupacis A, Carruthers G et al. Interaction between phenytoin and cyclosporine following organ transplantation. Transplantation 1984; 38: 304-5.

196. Jones K, Hakim M, Wallwork J et al. Serious interaction between cyclosporin A and sulphadimidine. Br Med J 1986; 292: 728-9.

197. Carstensen H, Jacobsen N, Dieperink H. Interaction between cyclosporin A and phenobarbitone. Br J Clin Pharmacol 1986; 21: 550-1.

198. Morgenstern GR, Powles R, Robinson B et al. Cyclosporine interaction with ketoconazole and melphalan. Lancet 1982; ii: 1342-3.

199. Gumbleton M, Brown JE, Hawksworth G et al. The possible relationship between hepatic drug metabolism and ketoconazole enhancement of cyclosporine nephrotoxicity. Transplantation 1985; 40: 454-5.

200. Ptachcinski RJ, Carpenter BJ, Burckart GJ et al. Effect of erythromycin on cyclosporine levels. New Engl J Med 1985; 313: 1416-7.

201. Kessler M, Louis J, Renoult E et al. Interaction between cyclosporin and erythromycin in a kidney transplant patient. Eur J Clin Pharmacol 1986; 30: 633-4.

Chapter 2

Psoriasis

Aspects of pathomechanisms and therapeutic modulation

Summary

The spectrum of clinical manifestations of psoriasis are presented with a description of the histopathology of the different morphological variations.
These data and currently known array of abnormalities that are observed in the spectrum of manifestations in psoriasis such as hyperproliferation, dyskeratinization, vascular alterations, the role of immune cells [1,2] and other mediators of inflammation are surveyed to explain some of the aspects of the pathomechanisms in psoriasis. In order to obtain an overview of the present state of pharmacological manipulation of these phenomena the literature on currently used therapies, some experimental approaches and their suspected mode of action, clinical results and adverse effects is reviewed.

Introduction

Psoriasis is a commonly occurring skin disease with a prevalence of about 2% and an equal sex distribution in Western Europe. Although considerable effort has been directed into research on the pathogenesis of psoriasis, the exact causal factor of the disease remains elusive.
Three suppositions for a mode of heridity are postulated. These are disease heterogeneity, polygenic determination and autosomal dominant inheritance with incomplete penetrance [3].
Apart from this genetic component, triggering factors can be recognized. After exogenous (mechanical) traumas like itching or endogenous luxating moments such as (focal) infections, endocrine inbalance, psychogenic stress or the use of particular drugs (lithium, ß blockers) the skin of susceptible individuals may show psoriasis or psoriasiform reactions (the isomorph Koebner phenomenon). Special attention has been drawn to the immunopathogenesis of psoriasis which offers an attractive model to explain many of the observed abnormalities such as epidermal hyperproliferation, dyskeratinization and inflammation. An inflammatory infiltrate together with a dysregulation in the production of cytokines [4-6] may also contribute towards the clinical presentation of the disease.

Clinical manifestations

Clinically, patients with psoriasis present skin lesions accompanied by erythema and desquamation. Preferential locations of the disease are elbows, knees, sacral area and the scalp but the palms and soles and the flexures or nails may also be involved, be it with a modified presentation. The initial diagnosis is supported by routine procedures such as a gentle "grattage" which produces a characteristic silver-white lining (candle-wax appearance) and the removal of adherent scales easily results in pinpoint bleedings (Auspitz' sign) [7,8].

The considerable variation in the clinical presentation of the disease results in a wide range of psoriasiform patterns [7,8].

In **guttate psoriasis**, small erythemato-squamous lesions (diameter up to 1.5 cm) are typically located on the trunk and proximal part of the extremities. In children, it has a benign course but in adults it usually shows a more stubborn character.

In **annular psoriasis**, ring-formed lesions with an inactive central region are observed. However, patients with psoriasis usually present sharply demarcated lesions varying from a few centimeters (**nummular type**) to large areas (**plaque type**) with a variable degree of infiltration. In these most common variants which usually follow a chronic course preferential sites are generally affected.

In **erythrodermic psoriasis**, the individual lesions have fused to form a generalized pattern of redness and scaling. This form of psoriasis is rather uncommon.

Pustular psoriasis is characterized by sterile pustules occurring locally or generally. Psoriasis of the palms and soles (Andrews-Barber disease) and acrodermatitis continua of Hallopeau on fingers or toes are very resistant to treatment.

An acute reaction predominantly consisting of small pustules scattered over the entire erythematous skin has been described by Von Zumbusch [8].

Seronegative arthritis (**psoriasis arthropathica**) is an extracutaneous manifestation of psoriasis [7,8].

Histopathology

The variations of the histological changes in psoriasis highly depend on the clinical type and on the stage of the disease [9,10].

In the macroscopically **unaffected skin**, modest epidermal hyperplasia and hypergranularity together with a condensed horny layer can prelude (as potential pre-psoriasis) the development of clinical psoriasis.

In the newly developing **pinhead lesion**, moderate epidermal hyperplasia and acanthosis of a few rete ridges and focal dilatation of the epidermal intercellular spaces are observed. Some macrophages and lymphocytes invade the epidermal malpighian layer in this early phase.

Polymorphonuclear leucocytes (PMNLs) invading the epidermis are observed after a few days [11]. In the dermis a perivascular infiltrate consists of lymphocytes and macrophages with a few PMNLs, while there is papillary edema and dilatation of the capillaries.

In **guttate psoriasis**, a focal epidermal hyperplasia, spongiosis and parakeratosis are observed. The granular layer over these foci disappears and the invading PMNLs accumulate in a network of degenerated stratum spinosum cells [12]. In the dermis the capillaries spiral high into the tops of the edematous papillae (squirting papillae) [10]. Lymphocytes and PMNLs aggregate in the parakeratotic mounds and form a perivascular infiltrate.

The margin of a **psoriatic plaque** shows the most prominent and typical characteristics such as a regular elongation of the rete ridges with thickening in their lower portions, thinning of the suprapapillary area and absence of a granular layer. Above the basal layer two cell rows with many mitoses are observed [10]. In the upper stratum Malpighii there is edema and spongiform pustule formation. Parakeratosis and Munro microabcesses are present in the corneal layer. The dermal papillae are long and club-shaped and the dilated capillaries are turtuous. The infiltrate in the epidermis consists of PMNLs [11] and in the dermis a mild infiltrate consisting of mononuclear cells is visible [colour plates 7 and 8].

The histology of psoriatic **erythroderma** also shows acanthosis, parakeratosis and changes in and above the tops of the dermal papillae but here exudation and dilated capillaries are more prominent.

In typical **pustular psoriasis**, spongiform pustules of Kogoj are located in the stratum Malpighii as a result of increased exocytosis of PMNLs. When the pustules move upwards the PMNLs become pycnotic and form large intracorneal microabcesses. This process may develop so rapidly that there is only a slight epidermal hyperplasia. In pustular psoriasis also dilated vessels in the edematous dermal papillae are surrounded by an infiltrate with lymphocytes and some PMNLs [10].

Microcirculation

An integral component of the psoriatic lesions are the microcirculatory vessels of the horizontal plexus in the dermis and the capillary loops [13,14]. The capillaries become dilated and tortuous in early lesions. Light microscopy examination shows that the capillary loops in psoriasis display the characteristics of venous capillaries with single or multilayered basal membrane material in the wall and the presence of bridged fenestrations in the endothelial layer. Endothelial cell gaps are present particularly in the postcapillary venules. These gaps may be responsible for the loss of plasma proteins and exocytosis of lymphocytes [15].

Electron microscopy

Detailed information on the ultrastructural pathology of psoriasis is now available [7,12,16]. The surface of a skin lesion shows a discontinous arrangement of scales and wide intercellular gaps. Filiform protrusions are observed around keratinocytes at all levels, which may be a sign of immaturity due to the higher metabolic activity in psoriatic skin and due to accelerated upward transit of the cells. The higher metabolic activity may be concluded from the increased number of cell organelles like mitochondriae, ribosomes, Golgi apparatus and a prominent endoplasmic reticulum. The increased volume of the psoriatic lesion is caused by hyperplasia (increase in cell number) and hypertrophy (increase in cell size by edema). Parakeratosis (the persistence of nuclear residues), delayed flattening of the cells and irregular thickness of the cell membrane are also signs of immaturation. In psoriasis, the cytoskeleton, which is the structural keratin framework important for cell shape and intracellular compartmentalization is abnormal. The number of tonofilaments is reduced, the depolimerization of microfilaments in the corneal layer is absent and the anchoring of tonofilaments in the microtubules is chaotic. The number of

desmosomes is reduced, whereas the gap junctions have increased in the upper layers. The relevance of virus-like particles observed in psoriasis has not yet been clarified [17].

Pathomechanisms

Two main approaches on the pathomechanisms in psoriasis have been proposed. These are a primary metabolic abnormality and a primary immunologic dysregulation [6].

Metabolic aspects

In psoriatic lesions, keratinocytes show a range of biochemical abnormalities. Although an abnormal proliferation may be genetically controlled, gene-mapping studies have not yet provided more information on a distinct modification at this level [3]. In the cytosol, several compartments are involved in an aberrant metabolism. In the Golgi apparatus increased glycosylation occurs, e.g. the fucose incorporation into glycoprotein is 3 times higher. The lysosomes produce 20-30 times more ß-glucosidase and arylsulphatase A and B. Mitochondrial enzyme activity is increased. The lipid content of the plasma membrane is increased [8]. Transmembranous signal transducing systems are altered [5]. Adenylate cyclase-cAMP, guanylate cyclase-cGMP, phospholipase C-diacylglycerol/inositol 1,4,5 triphosphate and epidermal growth factor-tyrosine kinase are all altered. As a result intracellular protein phosphorylation is increased and this is associated with enzyme activation (orthine decarboxylase and phospholipase A_2). The keratins of the cytoskeleton and cornified cell-envelope are grossly altered. The suprabasal 65-67 kD keratins are reduced or absent, whereas the amount of 50 and 58 kD keratins is decreased in the basal layer but increased weakly in the supralayers [8]. For high enzyme activity more calcium (free or protein bound) is needed. The Ca2+ binding protein, Calmodulin, is increased in psoriatic skin [19]. External stimuli such as growth factors and hormones induce biochemical changes which in turn function as a messenger system to various tissues or cell compartments.

Cell functions and cell-cell interactions

The main focus of investigation has been epidermopoiesis for considerable time [6]. Histologically besides keratinocytes other cell types are also relevant in psoriasis. In

psoriasis the germinative pool of actively cycling keratinocytes consists of 2-3 cell layers instead of one and the production rate is calculated to be 20 times higher than that in normal skin. The cell cycle is apparently normal in psoriasis but the migration from the basal layer until desquamation is approximately 10 times faster [8].

An increase of metabolic products (hydroxyproline, uronic acid, glycosaminoglycans) and the occurrence of less cross-linked collagen indicate that fibroblasts also play a role. In vitro, fibroblasts can induce hyperproliferation of epidermal cells [19]. The action of interferon (IFN) -gamma and interleukins (ILs) on the endothelial cells results in a derangement of the vascular pattern.

In the formation of micro-abcesses and overt pustulosis, accumulation of PMNLs occurs [11,20,21]. The number of dendritic cells and lymphocytes in the epidermis in psoriatic skin suggests an ongoing immunological process (cell-mediated immune response) [5,6,22].

As a putative immunologic stimulus in psoriasis many candidates have been suggested. These include auto-immunogens like a stratum corneum derived fraction and allo-immunogens such as retrovirus protein P27 [23]. Cells with dendritic morphology, Langerhans cells are supposed to be accumulated in the skin for antigen presentation [24]. The lymphocytes infiltrating into the (sub)epidermis are activated T-cells. The T-cell helper/suppressor ratio depends on the clinical state but the T-cell helper/inducer subset forms the majority [5]. Activated T-cells secrete cytokines like IL-2, that maintain and control the immune response but are also thought to stimulate epidermal growth [25].

Keratinocyte-lymphocyte interactions are considered to play a major role in psoriasis. One of the intergrins namely lymphocyte function associated antigen-1 (LFA-1) reacts with intercellular adhesion molecule-1 (ICAM-1) of activated keratinocytes mainly in those parts of the epidermis that overlay the top of the dermal papillae, thereby recruiting lymphocytes from the circulation [26]. Immunomodulating drugs like CyA which interfere with IL-2 dependent T-cell proliferation are thought to slow down keratinocyte proliferation in psoriasis.

For intercellular communication many mammalian cells secrete substances into the extracellular matrix. These mediators can also be involved in adhesion, growth regulation, cell migration and vasodilatation in the skin [27,28]. In psoriasis many molecules are suspected to play a role in the induction of abnormal proliferation and inflammation [5].

The family of eicosanoids, which have inflammatory mitogenic properties also play a role. Some of the metabolites are elevated in psoriasis. Leukotrienes, especially LTB_4, are chemoattractants for PMNLs [11]. Prostaglandines like PGE_2 and PGF_{2a} cause vasodilatation and probably epidermal proliferation [5,6].

Platelet activating factor (PAF) activates cell functions in combination with phospholipase C and Epidermal Growth Factor (EGF). Mononuclear cell derived lymphokines effect mitotic activity and parakeratosis. Interleukins from Langerhans cells, granulocytes and keratinocytes cause inflammation (granulocyte immigration, erythema and edema) and are able to activate keratinocytes, lymphocytes as well as fibroblasts and endothelial cells [5]. Complement factors deposited in psoriatic epidermis may be activated by anti-stratum corneum antibody-stratum corneum antigen complex formation. Some of these are chemoattractants for PMNLs [23]. Interferons, derived from T-cells (IFN-gamma) and from monocytes/macrophages (IFN-α) are apparently functionally active in psoriatic skin [6,29]. Gamma interferon induces the expression of HLA-DR on keratinocytes [30], increases the expression of HLA-DR on Langerhans cells and endothelial cells and induces the expression of intergrins. Intergrins are glycoproteins that function as cell surface receptors that play a role in the adherence of lymphocytes onto endothelial cells, keratinocytes, fibroblasts and dendritic cells [31,32]. All these factors are known to play a role in immunologic inflammation in psoriasis.

Recent investigations on the possible role of dentritic cells in the psoriatic skin suggest an important role of these cells in psoriasis [33], which may enable us to find a path in this complex labyrinth of data.

Current therapies

Topical treatment

Topical application of drugs is the first choice in the treatment of psoriasis. Especially tar preparations, dithranol and corticosteroids are of value as standardized regimes [7,8].

A - Tar preparations [34,35]. Coal tar, a product of dry distillation of bituminous coal (derivatives: pix lithantracis and solutio carbonis detergens) and wood tar (pix liquida) a residue of dry distillation of juniper, pine or birch are a mixture of aromatic hydrocarbons. They are used in ointments, shampoos and bath formulati-

ons and in combination with dithranol (Ingram regimen) or combined with ultraviolet radiation (Goeckerman therapy) [36].

The effectiveness of these compounds in psoriasis is possibly due to an inhibition of keratinocyte mitosis and subsequently of the keratinization process and an anti-pruritic effect. The tars are potential carcinogens probably due to the induction of the mono-oxygenase arylhydrocarbonhydroxylase but at the concentrations used in treatment schedules this adverse effect is minimal. Forty-one out of 1585 (2.6%) patients treated with tars developed non-melanoma skin cancers during a follow-up period of 10-25 years [33]. Other unwanted reactions include irritation, folliculitis, phototoxicity and possible contact sensitization [37] or photo contact sensitization. These aspects together with the brownish colour and the odour limit the use of tars.

B - Dithranol (1,8 dihidroxy-9-anthrane, syn. cignolin, anthralin) is a yellow, cristalline powder soluble in ether, benzol, chloroform and paraffin. It is insoluble in water. It is soon oxidised and inactivated by light, high temperature, zinc-ions and basic pH. Classically, 0.1-3% dithranol in vaseline is applied for 24 hours. The dithranol concentration is slowly increased until the desired therapeutic effect is obtained [7,8,39]. In the short-contact regimen up to five times higher concentrations are used for 10-20 minutes [39]. The suspected mode of action in psoriasis is via suppression of RNA synthesis, inhibition of glycolysis and the suppression of mitochondrial metabolism. It is also cytotoxic to the upper epidermal layers [40]. The possibility of irritation and the purple coloured oxidation products require careful instructions to the patients for optimal compliance.

C - Glucocorticosteroid hormones for topical application are in use since 1952 and available as many different ready-to-use preparations. They can be divided into four classes of increasing potency. Esterification and halogenation of the steroid molecule provide more potent preparations. For clinical application the area, the location and the duration of treatment are relevant for an optimal benefit-risk ratio. Plastic occlusion and intralesional injections have a special place in recalcitrant psoriatic plaques [7,8,41]. The main mechanism of action is thought to be that after penetration, corticosteroids pass through cell membranes to bind to cytosolic receptor proteins. The steroid-receptor complex then enters the nucleus where it

binds to DNA. This results in an a altered mRNA transcription, which in turn stimulates or inhibits specific protein synthesis. The phospholipase inhibitor, lipocortine is produced and interleukin-1 formation slowed down. Further, the immigration of inflammatory cells is reduced, the antigen presentation is inhibited, possibly via altered Langerhans cell function [42] which arrests the clonal T-cell expansion. Vasoconstriction, inhibition of DNA synthesis and mitosis make them potent anti-psoriatic drugs. A rapid (first pass) biotransformation to inactive compounds yields a topical steroid with minimal (unwanted) systemic effects. Local adverse effects are athrophy, striae, ecchymoses, infections and perioral dermatitis. Tachyphylaxis (acute intolerance) is known [43]. The relapse rate of psoriasis after stopping is high and occurrence of severe pustular reactions in this context are feared. Moreover systemic effects on the pituitary-adrenal axis are to be suspected by transdermal penetration after long-term use.

Systemic Therapy

When large areas of the body are involved in psoriasis or in case the disease is resistant to topical treatment, the use of other regimens, like ultraviolet radiation, retinoids and methotrexate is required.

A - Ultraviolet light (UV) therapy involves the use of non-ionizing radiation with wavelengths between 290 and 400 nm. The light sources used for this therapy have a high spectral output in a selected range, UVB (290-320 nm) or UVA (320-400 nm). Photochemotherapy combines UVA and oral photo-absorbers like 8 methoxy-psoralen (PUVA) [44].

In the skin UV light is absorbed by melanin, tryptophan, tyrosine, nucleic acids and photoactive substances and via excitation a range of chemical events is initiated. This results in a biological reaction related to skin type and dose and includes erythema, pigmentation, thickening of the epidermis, endothelial swelling, extravasation of erythrocytes, an increase of prostaglandins, a decrease of interleukin-1, damage of mitochondriae and keratinocyte cell-death.

The expression of Langerhans cell markers is inhibited and depleted [45]. The dermal infiltrate of lymphocytes decreases, possibly as a result of impaired interleukin-2 production [46]. Patient selection is important. Caucasians with skin

type II-V and an age between 20-60 years show good responses in case of uncomplicated forms of psoriasis like the plaque and guttate variant. Testing of the minimal erythema dose and careful dosimetry are relevant. Over 80% of the patients respond well in 20-40 sessions. With a 2 months maintenance therapy (one or two sessions a week) psoriasis can be controlled for 6-12 months. Continued use, however includes the potential risk associated with long-term UV-light exposure.

In day care centres, combination of UVA with coal tar (Goeckerman therapy) [47] or a psoralen bath can be carried out. PUVA can be combined with topical steroids or retinoids (re-PUVA) [45]. Main exclusion criteria for PUVA-therapy are abnormal liver functions and cardiovascular disease. Other contra-indications for phototherapy are the use of photo-sensitizing drugs, photo-allergy, diseases with a known photo-reactivity like lupus erythematosus or herpetic infections and a history of treatment with arsenic, ionizing radiation or tumors.

Side-effects are itching, hyper- and hypopigmentation and long-term effects such as premature aging (fragmentation of elastic fibres), actinic keratosis to overt skin cancer including melanoma [45] and in uncontrolled use acute reactions like erythema and burned skin. Tumor incidence seems to correlate with the cumulative UV dose (J/cm^2) and a combination of risk factors like the use of arsenic or tar [48]. The side-effects of psoralens (nausea, headache, dizziness and UV sensitivity after exposure to the artificial light source) must be added to those of UV therapy alone.

B - Aromatic retinoids. Etretinate and its principal free acid metabolite acitretin are synthetic vitamin A (retinol) derived preparations [48-51]. After oral intake, retinoids are absorbed from the intestinal tract (maximum 40%), transported by albumin and lipoproteins and metabolized in the liver. The main metabolite binds to cellular retinoid acid binding protein (CRABP). The long elimination time of etretinate is explained by storage in fat tissue [52].

The antipsoriatic effect is supposed to be multifactoral and includes the modulation of cell proliferation by a decreased mitotic rate. An influence on the keratinization process is deduced from an inhibition of the cornified cell envelope synthesis and a high number of keratohyalin granules. The modulation of a number of regulating

processes takes place such as inhibition of ornithine decarboxylase and reduced polyamine synthesis, a higher post-translational glycosylation and production of proteoglycans, next to an increase of type II cAMP dependent protein kinase and reduced angiogenesis. Immunomodulation and suppression of inflammation occur via migration inhibition of polymorphonuclear neutrophils and functional inhibition of lymphocytes, macrophages, Langerhans cells and a decrease in IFN production and arachidonic acid metabolism [53,54]. Retinoids can be effective especially in the pustular and erythodermic variants of psoriasis. A dose of 0.5-1 mg/k/d can normalize psoriatic skin within 3-6 weeks. Hereafter a maintenance therapy for 3-6 months is advised. About 6 months later 70% of the patients show a relapse. Forty percent are non-responders [55]. Main exclusion criteria are pregnancy because of teratogenicity, abnormal liver function and hyperlipidemia. The side-effects are muco-cutaneous complaints like erythema, irritation of mucous membranes (cheilitis, rhagades, dryness), stickiness and athrophy of the skin, peeling palms and soles, alopecia and multiple extra-cutaneous effects such as ophthalmologic disorders, liver toxicity, hyperlipidemia and cartilage degradation (preterm ossification of epiphyseal discs). Effective contraceptive measures are necessary for 2 years after stopping the drug [55].

C - Methotrexate (MTX, amethopterin, 4-amino-4-deoxy-N10-methylpteroylglutamic acid) is a folic acid antagonist. It inhibits dihydrofolate reductase and thus prevents DNA synthesis, blocks mitosis and lethally damages epidermal cells and interferes with protein synthesis. An inhibitory effect on the immune system has been reported [56]. Though intestinal function is relevant for the availability of (oral) MTX, blood serum levels are of little value in monitoring the effectiveness. The plasma half-time is 2 h.

About 50% of circulating MTX is bound to albumin. It is excreted by the kidneys (50-80% in 24 h) but a high output of alkaline urine is imperative. MTX is used for severe or disabling psoriasis and psoriatic arthritis, though there are many exclusion criteria. Several intermittent, low oral dose schedules are in use with an advised maximum dose of 25 mg per week. After a clearing phase, MTX can be continued for more than a year (maintenance period) [7,8].

Rebound reactions or tachyphylaxis are not reported. The effect of topical MTX is

hampered by a low percutaneous penetration.

Exclusion criteria for use of MTX are liver or renal dysfunction, pregnancy, peptic ulcer, excessive alcohol intake, anaemia, thrombopenia, leucopenia and interfering medication. Many side-effects of MTX are known. Subjective complaints include nausae, vomiting, abdominal pain, decreased appetite, fatigue, headache, dizziness, loss of libido, impaired memory and in particular hematopoietic suppression. Hepato-toxicity (cirrhosis) is monitored by liver function tests and liver biopsies. The predictive value of these parameters, however, is still under investigation [57,58]. The risk of (skin) malignancies seems only of theoretical value. MTX pneumonitis is rare on the low doses used for antipsoriatic treatment. Foetotoxicity is only reported in the first trimester of pregnancy [56]. Notwithstanding these facts and many contra-indications, MTX is regarded to be a safe drug if the "MTX guidelines" are observed [59].

Apart from the above mentioned established therapies several new drugs are under investigation for psoriasis. Two of the most promising are vitamin D formulations and fumaric acid.

A - The vitamin D calcitriol (1α, 25-dihydroxyvitamin D_3) and its analogues are under investigation for their effects after some cases with hypocalcemia-induced psoriasis were published. The skin appeared to be a target organ for calcitriol in addition to the intestine and bones, in regulating calcium metabolism. On the basis of in vitro studies and preliminary studies in men, this agent should be highly effective on hyperproliferative skin diseases. Its suspected mechanism of action is the regulation of the terminal differentiation of keratinocytes and modulation of the dermal inflammatory infiltrate. Side-effects are stones in the urinary tract and calcification of blood vessels. Topical dosing seems preferable to bypass these effects [60-62].

B - Fumaric acid (FA) is used as combination of sodium salts of the mono-ethyl ester and dimethyl-ester with or without a diet in the treatment of psoriasis. A deficiency of fumaric acid could not be demonstrated in psoriatics. The mechanism of action is possibly an anti-mitotic effect. Recent open and double-blind studies showed that oral FA therapy is only effective after about 4 months. Topical

treatment with FA formulations showed a low response. FA esters have severe side-effects such as flushing, dizziness, fatigue, pain of the upper digestive tract, leucopenia (due to a decrease of CD8+ T-lymphocytes) and nephropathy that turned out to be irreversible in some cases. Up till now the success of this therapy initiated by Schweckensiek (1959) [63] and regarded by the public as a "natural" therapy remains unproven. The toxicity and the teratogenic effects have not been quantitated as a consequence, the benefit-risk ratio has not been determined as yet [64].

The action mechanism(s) of all the drugs described above on the metabolic and immunologic aspects of psoriasis cannot be clearly separated but can be divided into three major groups:

1) Influence on metabolic process: tar, dithranol, fumaric acid, calcitriol
2) Influence on immunologic aspect: steroids, UV
3) Influences on metabolic and immunologic aspects: retinoids, methotrexate

On the basis of our current knowledge on the action mechanism(s) of CyA (Chapter 1), the drug would best fit in group 2.

It is too early to conclude which point of intervention, either the metabolic or the immunologic will be more effective, irrespective of the question whether this theoretical approach is the final truth.

Aim of the study

Although a large therapeutic arsenal of conventional drugs is available to treat patients with psoriasis, a group of patients still exists that fulfill the inherent exclusion criteria or present with subjective or objective side-effects. This necessitates the need for controlled studies with potential new antipsoriatic drugs like cyclosporin A. In this thesis patient-oriented studies on the treatment of severe psoriasis vulgaris with systemic low-dose and topical cyclosporin A are presented in an attempt to answer the following questions.

A - What is the efficacy of short-term low-dose cyclosporin A in patients with severe, recalcitrant psoriasis ? (Chapters 3 and 4)

B - Is there a preferential dose regimen for long-term treatment, either continous or intermittent ? Can the combination with a conventional drug like etretinate produce

an additive positive effect ? (Chapter 5)

C - Can topically applied cyclosporin A be effective in dermatologic disorders such as psoriasis ? (Chapter 6)

D - What are the side-effects of orally administered cyclosporin A ? How can nephrotoxocity be monitored ? What are the recommended guidelines for the practicing dermatologist for using cyclosporin A ? (Chapters 7 and 8)

References

1. Bos JD, Kapsenberg ML. The skin immune system (SIS). Its cellular constituents and their interactions. Immunol Today 1986; 7: 235-40.
2. Nickoloff BJ, Griffiths CEM. Lymphocyte trafficking in psoriasis. J Invest Dermatol 1990; 95: 358-78.
3. Wuepper KD, Coulter SN, Haberman A. Psoriasis Vulgaris: A genetic approach. J Invest Dermatol 1990; 95: 28-48.
4. Van Konniko N, Ree HJ, Dinarello CA et al. Interleukin-1 (IL-1) is present in psoriatic plaques. J Invest Dermatol 1987; 88: 499.
5. Bos JD. The pathomechanisms of psoriasis; the skin immune system and cyclosporin. Br J Dermatol 1988; 188: 141-56.
6. Fry L. Psoriasis. Br J Dermatol 1988; 119: 445-63.
7. Roenigk HH, Maibach HI Eds. Psoriasis M Dekker Inc. New York 1985.
8. Mier PD, van de Kerkhof PCM Eds. Textbook of psoriasis. Churchill Livingstone, Edinburgh 1986.
9. Ackerman B. Psoriatiform dermatitis. In: Histologic diagnosis of inflammatory skin disease. Lea & Febiger, Philadelphia 1978; 250-60.
10. Lever WF, Schaumberg-Lever G. Psoriasis. In: Histopathology of the skin. 6th edition, JB Lippincott Comp. Philadelphia 1983; 139-46.
11. Chang A. Polymorphonuclear leucocytes in psoriasis. Thesis, Nijmegen, The Netherlands 1989.
12. Brody I. Alterations of clinically normal skin in early eruptive guttate psoriasis. A light and electron microscopic study. J Cutan Pathol 1978; 5: 219-33.
13. Braverman IM. Ultrastructure and organisation of the cutaneous microvasculature in normal and pathologic states. J Invest Dermatol 1989; 93: 28-98.
14. Braverman IM, Sibley J. The role of microcirculation in the treatment and pathogenesis of psoriasis. J Invest Dermatol 1982; 78: 12-7.
15. Chin YH, Falanga V, Chai JP. Lymphocyte adhesion in psoriatic dermal endothelium: mechanism and modulation. J Invest Dermatol 1990; 95: 298-318.
16. Mahrle G. Ultrastructural problems in psoriasis. In: Kröger H, Stuttgen G Eds. Current research problems in psoriasis. Grosse, Berlin 1984: 53-8.

17. Iversen OJ. The expression of retrovirus-like particles in psoriasis. J Invest Dermatol 1990; 95:418-38.
18. Tucker WFG, Macneil S, Bleehen SS et al. Biologically active calmodulin levels are elevated in both involved and uninvolved epidermis in psoriasis. J Invest Dermatol 1985; 85: 450.
19. Priestley GC, Loid R. Fibroblast-keratinocyte interactions in psoriasis: failure of psoriatic fibroblasts to stimulate keratinocyte proliferations in vitro. Br J Dermatol 1990; 123: 467-72.
20. Tagami H, Iwatsuki K, Takamatsu H. Psoriasis and leucocyte chemotaxis. J Invest Dermatol 1987; 88: 18s.
21. Tonnesen MC. Neutrophil-endothelial cell interactions: mechanisms of neutrophil adherence to vascular endothelium. J Invest Dermatol 1989; 93: 538-88.
22. Ramirez-Bosca A, Martinez-Ojeda L, Valcuende-Cavaro F et al. A study of local immunity in psoriasis. Br J Dermatol 1988; 119: 587-96.
23. Krogh HK. Antibodies in human sera to stratum corneum. Int Archs Allergy Appl Immunol 1969; 36: 414-26.
24. Breathnach SM. The Langerhans cell. Br J Dermatol 1988; 119: 463-9.
25. Paliard X, de Waal Malefijt R, IJssel H et al. Simultaneous production of IL-2, IL-4 and IFN-gamma by activated CD4+ and CD8+ T cell clones. J Immunol 1988; 141: 849-55.
26. Dustin MI, Singer KH, Tuck DT et al. Adhesion of T-lymphoblasts to epidermal keratinocytes is regulated by interferon-y and is mediated by intercellular adhesion molecule. J Exp Med 1988; 167: 1323-40.
27. Greaves MW. Inflammation and mediators. Br J Dermatol 1988; 119: 419-26.
28. De Mare S, de Jong E, van Erp PEJ et al. Markers for proliferation and keratinization in the margin of the active psoriatic lesion. Br J Dermatol 1990; 122: 469-76.
29. Barker JNWN, Allen MH, MacDonald DM. Alterations induced in normal skin by in vivo interferon-gamma. Br J Dermatol 1990; 122: 451-8.
30. Barker JNWN, Navsaria HA, Leigh IM et al. Gamma-interferon induced human keratinocyte HLA-DR synthesis: the role of dermal activated T-lymphocytes. Br J Dermatol 1988; 119: 567-72.

31. Heng MCY, Allen SG, Chase DG. High endothelial venules in involved and uninvolved psoriatic skin: recognition by homing receptors on cytotoxic T-lymphocytes. Br J Dermatol 1988; 118: 315-26.

32. Chin YH, Falang V, Streilein JW et al. Lymphocyte recognition of psoriatic endothelium: evidence for a time-specific/ligand interaction. J Invest Dermatol 1989; 93: 828-78.

33. Prens EP, Benne K, van Joost TH et al. The autologous mixed epidermal cell-T lymphocyte reaction is elevated in psoriasis: A crucial role for epidermal HLA-DR+/CD1a-antigen-presenting cells. J Invest Dermatol (in press).

34. Young E. The external treatment of psoriasis: a tar controlled investigation of the effects of coal tar. Br J Dermatol 1970; 82: 510-5.

35. Müller SA. Topical treatment of psoriasis with tar. Acta Dermatovenereol (Stockh) 1983; 1128: 7-10.

36. Perry HO, Saderstrom CW, Schulze RW. The Goeckerman treatment of psoriasis. Arch Dermatol 1986; 68: 178-82.

37. Roesyanto ID, van den Akker ThW, van Joost Th. Wood tar allergy, cross-sensitization and coal tar allergy. Contact Dermatitis 1990; 22: 95-8.

38. Ashton RE, Andre P, Lowe NJ. Anthralin: Historical and current prospectives. J Am Acad Dermatol 1983; 9: 173-6.

39. Lowe NJ, Ashton RE, Koudsi H et al. Anthralin for psoriasis. Short-contact anthralin with topical steroid and conventional anthralin. J Am Acad Dermatol 1984; 10: 69-72.

40. Parish LC, Millikan LE, Witkowski JA. The modern story of anthralin. Int J Dermatol 1989; 28: 373-4.

41. Polano MK. Corticosteroiden in de dermatologie. N Tijdsch Geneesk 1977; 121: 2083-8.

42. Asworth J, Booker J, Breathnach SM. Effects of topical corticosteroid therapy on Langerhans cell antigen presenting function in human skin. Br J Dermatol 1988; 118: 457-70.

43. Du Vivier A, Stoughton RB. Acute tolerance to effects of topical corticosteroids. Br J Dermatol 1976; 94, Suppl 12: 25-31.

44. Gupta AK, Anderson TF. Psoralen photochemotherapy. J Am Acad Dermatol

1987; 17: 1703-34.

45. Wolff K. Side-effects of psoralen photochemotherapy (PUVA). Br J Dermatol 1990; 122, Suppl 36: 117-25.

46. Okamoto H, Hori OT, Malda M. Alterations of lymphocyte function by 8-methoxypsoralen and long-wave ultraviolet light radiation. II The effect of in-vivo PUVA on IL-2 production. J Invest Dermatol 1987; 89: 24-6.

47. Low NJ, Wortzman M, Breeding J et al. Coal tar photochemotherapy for psoriasis reevaluated. J Am Acad Dermatol 1983; 8: 781-9.

48. Stern RS, Zierler S, Parrish JA. Skin carcinoma in patients treated with topical tar and artificial ultraviolet radiation. Lancet 1980; i: 732-5.

49. Saurat JH. Ed. Retinoids: New trends in research and therapy. Karger, Basel 1985.

50. Orphanos CE. Retinoide: der neue Stand. Hautarzt 1989; 40: 123-9.

51. Brindley CJ. Overview of recent clinical pharmacokinetic studies with Acitrecin (Ro10 1670, Etretin). Dermatologica 1989; 178: 79-87.

52. Digiovanna JJ, Zech La, Ruddel ME et al. Etretinate persistant serum levels after long-term therapy. Arch Dermatol 1989; 25: 246-51.

53. Vahlquist A, Törmä H. Retinoids and keratinization: current concepts. Int J Dermatol 1988; 27: 81-95.

54. Dupuy P, Bagot M, Heslon M et al. Synthetic retinoids inhibit the antigen presenting properties of epidermal cells in vitro. J Invest Dermatol 1989; 93: 455-9.

55. Halioua B, Saurat JH. Risk: benefit ratio in the treatment of psoriasis with systemic retinoids. Br J Dermatol 1990; 122, suppl 36: 135-50.

56. Zachariae H. Methotrexate side-effects. Br J Dermatol 1990; 122, Suppl 36: 127-33.

57. Newman M, Holzman RS, Culubret M et al. Detection of hepatotoxicity associated with methotrexate therapy for psoriasis. Arch Dermatol 1989; 125: 1209-17.

58. O'Connor GT, Omstead EM, Zug K et al. The role of liver biopsies in patients receiving long-term methotrexate treatment. Arch Dermatol 1989; 125: 1218-24.

59. Roenigk HH, Auerbach R, Maibach HI et al. Methotrexate in psoriasis: revised guidelines. J Am Acad Dermatol 1988; 19: 145-56.

60. Smith EL, Pincus SH, Donovan L et al. A novel approach for the evaluation and treatment of psoriasis. J Am Acad Dermatol 1988; 193: 516-28.

61. Van de Kerkhof PCM, van Bokhoven M, Zultak M et al. A double-blind study of topical 1α, 25-dihydroxyvitamin D_3 in psoriasis. Br J Dermatol 1989; 120: 661-4.

62. Muller K, Svenson M, Bendtzen K. 1α, 25-dihydroxyvitamin D_3 and a novel vitamin D_3 analogue MC 903 are potent inhibitors of human interleukin 1 in vitro. Immunol Letters 1988; 17: 361-6.

63. Schweckendiek W. Heilung von psoriasis vulgaris. Med Monatschr 1959; 13: 103-4.

64. Nugteren-Huying WM, van der Schroeff JG, Hermans J et al. Fumaarzuurtherapie tegen psoriasis; een dubbelblind, placebo-gecontroleerd onderzoek. Ned Tijdschr Geneesk 1990; 134: 2387-91.

Chapter 3

Short-term use of cyclosporin A in severe psoriasis

This chapter is based on the following manuscript:

Short-term use of cyclosporin A in severe psoriasis.
Van Joost Th, Heule F, Stolz E, Beukers R.
Br J Dermatol 1986; 114: 615-20.

Summary

The effectiveness of cyclosporin A (CyA) in low dosages (mean 5 mg/kg/d) for short-term treatment of severe psoriasis was studied. Of five patients with severe progressive psoriasis vulgaris (mean PASI score 43.8), an almost complete remission in three patients, and a large reduction in PASI score in the remaining two patients, was obtained within 4 weeks. No important clinical side-effects were found but there was biochemical evidence of slight renal dysfunction in one patient. The mean percentage reduction in the PASI score was 84%. The results reported justify further study of CyA in the treatment of severe psoriasis.

Introduction

In psoriasis a number of aberrations of the immune system have been reported [1]. The cellular infiltrate in the clinically active psoriatic lesions may contain 30% activated T cells [1] and there is evidence of functional defect in T-lymphocytes [2].

CyA may interfere with T-cell functions, i.e. by blockade of the production of interleukins, in particular interleukin-2 [3]. Apparent responsiveness of psoriatic lesions to CyA has been described recently [4]. In a restricted number of patients with renal transplants and psoriasis, it has been reported that the skin lesions improved significantly during CyA treatment [5,6].

We present here a pilot study aimed at determing the effectiveness of a short-term "crisis-intervention" treatment of four weeks with CyA in five patients. In addition, the response to CyA was evaluated during a second period of 4 weeks.

Methods

Patients

Five patients (Table 1) were selected on the following criteria: unequivocal clinical and

histopathological diagnosis of chronic plaque form psoriasis, severe disease, long duration of disease (mean 27 years) and resistance to conventional anti-psoriatic therapy (topical therapy including steroids, systemic therapy with PUVA or retinoids or both). Four patients had been treated previously with methotrexate with variable results.

On entering the study, all the patients exhibited progressive psoriasis with serious physical and social disabilities. Patients were excluded from the study if they were pregnant or suffering from infection, malignancy, impaired renal function (serum creatinine $>$ 110 μmol/1), impaired liver function, uncontrolled hypertension (age 18-50 RR $>$ 150/95, age 50-60 RR $>$ 60/100), epilepsy, malabsorption syndrome or drug or alcohol abuse. Other criteria for exclusion were: treatment with methotrexate, retinoid or PUVA within one month, or topical anti-psoriatic agents within 2 weeks before the start of the trial.

Clinical evaluation before and during therapy was carried out using the Psoriasis Area and Severity Index (PASI) [7] [Addendum 1]. The PASI score increases in units of 0.1 from 0.0 (no lesions), to 72.0 (complete psoriatic erythroderma of the severest possible degree). The PASI score was recorded before the start of the trial and at weekly intervals during therapy.

On entering the study all five patients had a PASI score $\geq$ 28 (mean 43.8) (Table 1). CyA (Sandimmune^R, 100 mg/ml) was given orally in two daily doses on the basis of body weight. Full blood count, renal and liver function and blood pressure were measured at weekly intervals. Determinations of trough blood CyA concentrations using a cyclosporin RIA-Kit, (Sandoz Ltd, Basel, Switzerland) were performed weekly (Table 2).

The initial dose of CyA (4.4-6 mg/kg/d) was given for 4 weeks (Table 2). In the second 4-weeks period (weeks 5-8) the dose of CyA was gradually adapted for individual patients, in particular in relation to the PASI score (Table 2). No other anti-psoriatic treatment was given.

Results

The PASI scores in the patients before entering the trial and after 1,2,4 and 8 weeks are given in Table 1. The dosages and trough blood concentrations of CyA are given in Table 2. Mean PASI scores, trough blood CyA concentrations and CyA dosages over weeks 1-4 are shown in Figure I.

First treatment period (weeks 1-4)

A low dose of CyA (mean 5 mg/kg/d Table 2) had a satisfactory effect in all five patients with severe psoriasis [colour plates 1 and 2]. In patient 1 a substantial fall in the PASI score was found within the first 2 weeks (53.2-8.4). In patients 4 and 5, within 2 weeks, the PASI scores fell by 53% and 40% respectively. The mean PASI score in the five patients after 2 weeks was 22.6 compared with 43.8 at start of the trial. The mean PASI score fell from 43.8 to 6.1 in the first 4 weeks of the treatment. This represents a mean improvement of 84%. The clinical response by the end of the first 4 weeks was most striking in patients 1 and 2 (98% and 97% reduction in PASI score, respectively, Table 1).

Second treatment period (weeks 5-8)

The decision was made to stop CyA in patient 1 during weeks 5 and 6, because of the striking remission (PASI score: 0.9). This resulted in an acute relapse within one week. Thereafter, the psoriasis reacted far more slowly to re-institution of CyA at a dose of 4.7 mg/kg/d (trough blood level: 530-590 ng/ml) (PASI score at 8 weeks: 10.3; Table 1). In patient 4, after increasing the dosage to 7.0 mg/kg/d (Table 2), there was a fall in the PASI score from 12.3 (week 4) to 1.3 (week 8). In the second period of 4 weeks the mean PASI score did not change substantially; falling from 6.1 to 4.7. During this period of the trial a low dose of CyA was found to be effective, giving excellent results in particular in patients 2 and 4. In patients 2, 3 and 4 a substantial improvement occurred in psoriatic nail lesions. In patient 4, with severe psoriatic arthropathy, a striking subjective and objective improvement was noticed ($\geq$40%).

Clinical side-effects, including mild reversible hypertension (160/100) (patients 1 and 4), and mild intermittent diarrhoea (patient 3), were observed. Clinically important disturbances of renal or liver function or blood count were not seen. Nevertheless, biochemical evidence of mild renal dysfunction was found in one patient (patient 4).

Discussion

We report here the effectiveness of CyA in crisis intervention therapy in five selected patients with severe, chronic and drug-resistant psoriasis. Mueller & Herrmann [4] first reported a dramatic response to CyA within one week in four psoriatic patients but the psoriatic lesions gradually returned to their previous severity within 2 weeks after stopping CyA. Müller and Graf [8] described four patients who received CyA with a striking improvement of severe psoriatic arthritis and of psoriatic skin lesions. These authors observed improvement of the arthritis in three out of the four cases and a striking reduction of the psoriatic skin lesions in all four cases in the first 2-4 weeks of treatment with CyA in high initial doses (about 900 mg/d). Three out of the four cases relapsed after the dosage of CyA was reduced 200-400 mg/d. In these studies no measurements of the clinical improvement in relation to blood concentrations of CyA were performed.

In our patients a tendency to a dose dependent response to CyA was seen in patients 1 and 4. In patient 3 a less striking response was seen (PASI score: 8.0 at week 8) with lower trough blood concentrations of CyA (160-250 ng/ml. In patient 5, however, despite a very low blood concentration (70 ng/ml at week 8, (Table 2)), the PASI score remained low (2.7).

The number of patients was too small for adequate experiments to determine optimal dosages. However, the present study shows that at dosages between 4.7 and 8.1 mg/kg/d (trough blood concentrations between 390 and 980 ng/ml), short-term therapy with CyA is of value as psoriasis "crisis intervention".

The pharmacokinetic mechanism in psoriasis is still unknown, but it is tempting to assume that modification of T-cell functions by CyA plays a central role in the response to CyA

treatment. However, further studies are required to investigate possible inhibitory effects of CyA on the abnormal proliferation of keratinocytes in psoriasis. Keratinocytes produce a cytokine (epidermal cell derived thymocyte-activating factor) which closely resembles interleukin-1 [9].

CyA acts in the preliminary phase of the immune response and it has been suggested that if long-lived populations of primed T-cells are operative, the beneficial response to the drug may become apparent after several months of treatment only [10]. Such a mechanism would explain the incomplete responses in our patients.

CyA can give rise to a variety of side-effects and, for the present, its use -like that of other immunosuppressants- must be contemplated only in severe psoriasis, which is physically or socially extremely disabling. Treatment of psoriasis and psoriatic arthritis with cytostatic drugs as methotrexate can also evoke a beneficial response within a reliable period, but numerous side-effects (in particular of the liver and bone marrow) are described [11]. We obtained a mean reduction in the PASI score of 84% after 4 weeks of treatment. Fredriksson and Petterson [7] reported a reduction of 63% after 4 weeks' treatment with retinoids in a group of 10 patients with severe psoriasis. A few possibilities were considered after the eighth week of treatment: (a) stopping CyA treatment; (b) trying a low maintenance dosage for a longer time and, (c) a low maintenance dosage of CyA in combination with other anti-psoriatic treatment. In our patients we decided after the eighth week to continue a low maintenance dose of CyA with no other treatment and further individual decreases in dosage, but maintenance of blood concentrations of $\geq$ 200 ng/ml. In patients 2 and 4, therapy with mean dose of 4 mg/kg/d was continued for a further 5 and 12 weeks respectively and was then stopped (PASI score in both cases was 0 at this point). In patient 2 the PASI score remained 0 two months after stopping CyA, without any other therapy. Patients 1 and 5 continued CyA therapy on a low dose regimen. In patient 3 (PASI score of 8 at week 8) the PASI score was reduced nearly to 0 after 10 further weeks on CyA at a dosage of 4.5 - 5.5 mg/kg/d (trough blood concentration $\geq$ 200 ng/ml). In this case, however, a local relapse of the skin lesions on the hands occurred when the dose of CyA was reduced below 4 mg/kg/d.

The results of the present study would appear to justify a further placebo-controlled double-blind study on the use of CyA in severe psoriasis. The design and the results of this study are described in Chapter 4.

Table 1. Reductions in PASI* scores in five patients with severe progressive psoriasis vulgaris, treated with cyclosporin A

Patient no.	Sex	Age (years)	PASI score before treatment	PASI score after treatment for: 1 week	2 weeks	3 weeks	4 weeks	Reduction in PASI score after 4 weeks (%)	PASI-score after treatment for 8 weeks
1	M	51	53.2	23.5	8.4	4.7	0.9	98	10.3**
2	M	73	32.3	29.8	26.4	12.0	0.9	97	1.1
3	M	55	58.0	43.2	36.5	13.2	10.0	83	8.0
4	F	48	28.2	13.8	13.5	12.6	12.3	57	1.3
5	F	40	47.5	34.8	28.4	18.0	6.5	86	2.7
Mean		53	43.8	29.0	22.6	12.0	6.1	84	4.7

* PASI =Psoriasis Area and Severity Index (Fredriksson & Petterson, 1978).
** Cyclosporin not given in weeks 5 and 6.

Table 2. Doses of cyclosporin A (mg/kg/d) and trough blood levels (ng/ml) (in parentheses) in five patients with severe progressive psoriasis

	Weeks 1-4				Weeks 5-8			
Patient no.	1	2	3	4	5	6	7	8
1	6 (600)	6 (720)	4.7 (770)	4.8 (890)	** (120)	** (60)	4.7 (530)	4.7 (590)
2	5.6 (700)	5.6 (670)	5.6 (650)	4.4 (610)	4.4 (610)	3.9 (—)	3.6 (—)	3.6 (—)
3	5.7 (—)	5.7 (390)	5.7 (430)	5.0 (450)	5.0 (480)	5.0 (520)	4.3 (250)	4.3 (160)
4	5.5 (530)	5.5 (460)	5.5 (490)	5.5 (430)	7.0 (410)	8.1 (370)	8.1 (750)	7.4 (980)
5	5.0 (210)	5.0 (210)	5.0 (250)	5.0 (250)	5.0 (240)	4.4 (—)	4.4 (170)	4.4 (70)
Mean	5.6 (510)	5.6 (530)	5.3 (518)	4.9 (526)	5.4 (372)	5.4 (317)	5.0 (400)	4.9 (450)

** In Case 1 cyclosporin was stopped during weeks 5 and 6 (see text).
— = Not estimated.

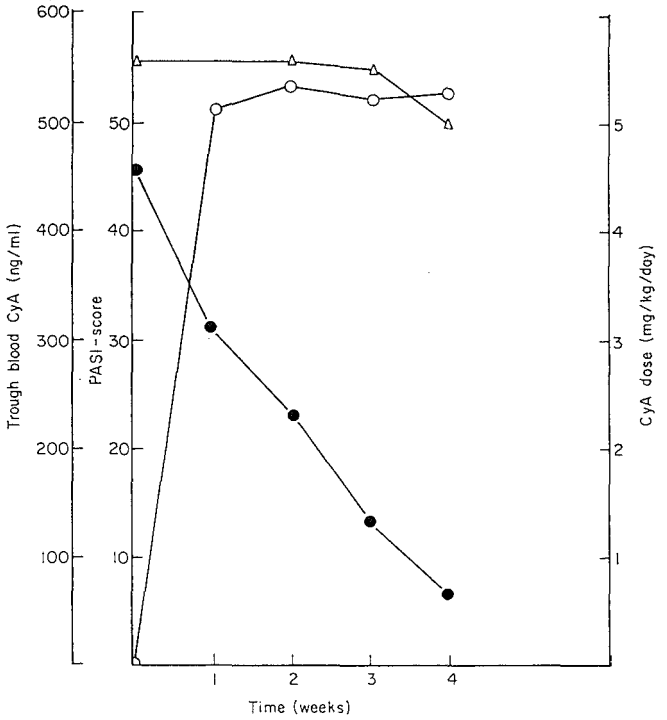


FIGURE 1. Mean CyA dose, trough blood CyA level and PASI score in five patients with severe psoriasis. ● Mean PASI score; ○ mean trough blood level of CyA (ng/ml); △ mean dosage of CyA.

References

1. Baker BS, Swain AF, Valdimarsson H et al. T cell sub-populations in the blood and skin of patients with psoriasis. Br J Dermatol 1984; 110: 37-41.
2. Gladman DD, Keystone EC, Russell ML et al. Impaired antigen-specific suppressor cell activity in psoriasis and psoriatic arthritis. J Invest Dermatol 1981; 77: 406-9.
3. Bendtzen K. Ciclosporin (cyclosporin A): Prototype of a new generation of immunosuppressive drugs. Allergy 1984; 39: 565-71.
4. Mueller W, Hermann B. Cyclosporin for psoriasis. N Engl J Med 1979; 301: 555.
5. Harper JI, Keat ACS, Staughton RCD. Cyclosporin for psoriasis. Lancet 1984; ii: 981-2.
6. Van Hooff JP, Leunissen KML, van der Staak W. Cyclosporin for psoriasis. Lancet 1985; i: 335.
7. Frederiksson T, Petterson U. Severe psoriasis-oral therapy with a new retinoid. Dermatologica 1978; 157: 238-44.
8. Müller W, Graf U. Die Behandlung der Psoriasis Arthritis mit Cyclosporin A, einem neuen Immunosuppressivum. Schweiz Med Wochenschr 1981; 111: 408-13.
9. Sauder DN, Charles S, Carter BS et al. Epidermal cell production of thymocyte activating factor (ETAF). J Invest Dermatol 1982; 79: 34-9.
10. Editorial. Cyclosporin in autoimmune disease. Lancet 1985; i: 909-11.
11. Oppolzer R, Diem E, Wolf G. Zur Differentialdiagnose und Therapy der Psoriasis-Arthritis. Zeitsch Hautkr 1976; 51: 131-42.

Chapter 4

Low-dose cyclosporin A effective in severe psoriasis: A double-blind study

This chapter is based on the following manuscripts:

Low-dose cyclosporin effective in severe psoriasis; A double-blind study.
Heule F, Meinardi MMHM, van Joost Th, Bos JD.
Transplantation Proceedings 1988; vol xx no. 3, suppl. 4 June: 32-41.
Low-dose cyclosporin A in severe psoriasis. A double blind study.
Van Joost Th, Bos JD, Heule F, Meinardi MMHM.
Br J Dermatol 1988; 118: 183-90.

Summary

Twenty patients with severe plaque psoriasis were selected to receive either low-dose cyclosporin A (CyA) or placebo (CyA vehicle) in a double-blind randomized trial at two centers. Within 4 weeks the mean reduction in the Psoriasis Area and Severity Index (PASI) in 10 patients receiving CyA (mean dose 5.5 mg/kg/d) differed significantly from the mean reduction in 10 patients receiving placebo. In eight patients given placebo a switch to CyA therapy resulted within 4 weeks in a mean reduction in PASI of 90%. In a total of 15 out of 18 patients given CyA (83%) (mean dose 5.6 mg/kg/d) there was an improvement of $\geq$ 75% in PASI within 4 weeks. In a 2-month tapering off phase a lower mean CyA dose (3 mg/kg/d) was effective in maintaining the reduced PASI scores in eight of nine patients. Four out of five CyA treated patients who entered a post-treatment observation phase had a relapse (PASI score $\geq$ 50% of score at baseline) after a mean interval of 6.5 weeks.

The most important side-effects were mild reversible hypertension in 5 of 18 patients (28%), and reversible elevated serum creatinine levels in 7 out of 18 patients (39%). We consider that further studies are justified in severe chronic psoriasis to establish suitable regimes for maintenance of remission in psoriasis with low doses of CyA or a combination of CyA with other anti-psoriatic agents.

Introduction

CyA selectively influences the function of lymphocyte subsets [1,2]. In a number of dermatologic conditions [3,4], over the past few years CyA has been used with more of less effects. In the treatment of psoriasis it is evidently a potent drug. Initially some case reports mentioned a remission of concomitant psoriasis when CyA was used in arthritis [5] or organ transplantation [6,7]. By that time the dosage schemes were high, namely 10 to 14 mg/kg/d. Later on open trials have demonstrated that lower dosages of 3 to 5 mg/kg/d have a significant beneficial effect in severe recalcitrant psoriasis [8-10]. A double-blind study [11], with a high-dose regime (14 mg/kg/d) showed that CyA was

significantly better than the placebo drug. We conducted a double-blind study in two academic hospitals in 20 patients with chronic plaque-form psoriasis of a therapy-resistant character.

In **phase 1** (weeks 1 to 4) low-dose CyA was compared to placebo to study the efficacy to induce a remission of the disease.

In **phase 2** (weeks 5 to 12) a stepwise tapering of the CyA dose in responders was performed to determine the lowest effective dose necessary to maintain the improvement or to prevent an exacerbation.

In **phase 3** (weeks 13 to 24) CyA therapy was stopped to study the interval till recurrence of complaints.

Methods

Selection of Patients. In each of the two centers, ten patients were selected: 13 females and 7 males. Inclusion criteria were a clinical and histologic diagnosis of chronic plaque psoriasis of a progressive character, over more than 10 years (Table 1).

Conventional therapy, eg, topical steroids, PUVA, oral methotrexate, or retinoids, singly or in combination, had been given with no or only temporary effects. Patient ages were between 20 and 70 years. Exclusion parameters were pregnancy or acute uncontrolled infection, either bacterial, viral or fungal, as well as impaired renal function with a serum creatinine over 100 μmol/l, bilirubin or liver enzymes more than twice the upper limit of the normal range, uncontrolled hypertension (ages 18 to 50 years BP 150/95 mmHg; ages 50 to 60 years, BP 160/100 mmHg), other diseases such as epilepsy, malabsorption syndrome, and past or present malignancies, and intoxication with abused drugs, alcohol, nephrotoxic drugs (e.g. amino glycosides or nonsteroidal anti- inflammatory drugs), and drugs known to affect the pharmacokinetics of CyA (ketaconazole, erythromycin, phenytoin, phenobarbitone, rifampicin, isoniazid or carbamazepin).

Active antipsoriatic treatment were stopped: methotrexate, retinoids or PUVA four weeks and topically applied agents two weeks before start of the trial.

Clinical evaluation

Improvement or worsening of the skin condition was analyzed with the Psoriasis Area and Severity Index (PASI) [12] (Addendum 1). This score system increases in units of 0.1 from 0.0 (no lesions) to 72.0 (complete psoriatic erythroderma of the severest possible degree). All patients started with a PASI of 20 or above.

Phase 1

Twenty patients were randomly treated with CyA of placebo during 4 weeks, in a double-blind set up. They were hospitalized for this period. CyA (Sandimmune^R, Sandoz Ltd. Basel, Switzerland) 1 ml solution contains 100 mg CyA powder or placebo (the vehicle consisting of olive oil and polyethylated oleic glycerin) was given in two equal daily doses (at 8:00 AM and 8:00 PM).

Daily doses were adjusted on the basis of body weight: $<$ 59 kg, 3 ml; 60 to 80 kg. 4 ml; $>$ 80 kg, 5 ml. The doses were reduced according to protocol by 1 ml if an unwanted change in criteria was noticed: (1) serum creatinine value rose above the baseline of 60 μmol/l, [13]; (2) serum potassium rose above upper limit of normal range; (3) an increase of serum bilirubin or liver enzymes above twice the upper limit of normal range; (4) hypertension unresponsive to antihypertensive therapy; or (5) whole blood trough levels of CyA above 900 ng/ml (reported by the nonblind investigator).

If the abnormal values did not normalize within 2 weeks, the CyA dose was further reduced by 1 ml. The test medication was withdrawn when these measures had no result or when subjects developed symptoms of infection.

Nonresponders were defined as patients who had a reduction in PASI of less than 50% at week 4 compared to their score at the start of the trial. When the test medication was stopped, the code was broken. Patients who had received placebo were switched to CyA

treatment in an open outpatient trial with the same dose schedule of CyA as in phase I.

Phase 2

The patients who responded with an improvement of more than 50% at the end of week 4 received the test medication for another 2 months (weeks 5 to 12) in a double-blind way. During this period the doses were reduced at two weekly intervals according to the schedule in Table 2. An increase of the PASI during the tapering process to a value equal or above 50% of the baseline value (before therapy) was called a relapse situation. When this happened the test medication was stopped and an alternative therapy was chosen.

Phase 3

Posttreatment observation period of 3 months. CyA treatment was stopped. Those who consented to receive no other antipsoriatic medication entered phase 3. If a relapse occurred patients were excluded. The PASI was measured monthly.

During phases 1 to 3 creatinine and potassium were measured at weekly intervals. Blood pressure, bilirubin and liver enzymes, urine analysis, and full blood count were measured every 2 weeks. Trough blood CyA concentrations 10 to 14 hours after the last dose of CyA were measured using the CyA RIA-Kit (Sandoz). Measurements were made at 1-week intervals in phase 1 and at 2-week intervals in phase 2.

Statistical analysis was performed using the Mann-Whitney U test to compare the changes in PASI values (score at the end of week 4 minus score at baseline). The same test was used to evaluate the blood pressure (systolic/diastolic) and creatinine values. The differences in the values of the period from week 0 to 4 were compared to the differences of weeks 0 to 4 in the CyA-treated and untreated groups. Changes within both treated and untreated groups of blood pressure and creatinine data (week 0 v weeks 4, 12, and 24) were assessed by the signed rank test (SRT).

Results

The doses and PASI value in patients receiving CyA are summarized in Fig. 1 and Tables

3 and 4.

The CyA dosage of patient 10 in week 2 and patient 2 in week 3 was reduced because the blood levels exceeded 900 ng/ml. This was not due to an overdose but appeared to be peak levels. A consistent relationship between the clinical response and CyA blood levels could not be found.

Phase 1

After the initial period of 4 weeks (phase 1) the number of nonresponding patients was 11. Their code was unsealed and all but one (patient 6) appeared to have received placebo. At the end of week 12 the code of the responders was broken; they all had received CyA. The mean percentage reduction in the PASI score at the end of week 4 in the group treated with CyA (72%) was significantly greater than the mean percentage reduction in the placebo group 3% ($p < .001$). In four patients in the placebo group (patients 13, 15, 17 and 19) worsening of the psoriasis was seen during phase 1.

The patient (patient 6) that did not react well (nonresponder) at week 4 improved on a higher dose of CyA after another 4 weeks (percentage reduction of PASI 79%). A slow reaction was seen in patient 7, who accidentally had received a lower dose of CyA (4 ml/d - 4.3 mg/kg/d) that did not correlate with his body weight (93 kg).

Phase 2

The mean percentage reductions of PASI in week 12 compared to the baseline values (for $n = 9$) was 82%. This means a further improvement of 10% (PASI reduction week 4, 72%). All nine patients had received CyA. In one patient (patient 2) a relapse was observed during week 12 (Table 4). In these nine patients a substantial improvement was observed in psoriatic nail lesions. The mean CyA dose during this tapering-off phase (weeks 5 to 12) was 3 mg/kg/d with mean CyA whole blood trough levels of 317 ng/ml. The mean CyA dosage during weeks 11 and 12 even went down to 1.4 mg/kg/d, which gave a mean blood level of 131 ng/ml.

Phase 3

At the start of this (posttreatment) phase of the trial, three of the remaining eight patients insisted on either continuation of CyA therapy (low-dose) or an alternative antipsoriatic therapy modality. Thus, only five patients entered phase 3 of the trial (Table 4, Fig 1C) In two patients a relapse was seen at week 16 (patients 7 and 9) two patients had relapsed at week 24 (patients 3 and 8), and one patient maintained a PASI of 2.1 (patient 1). It is worth mentioning that this last patient had the habit of taking a spoonful of cod liver oil every day.

Switch to CyA therapy in the placebo group

Eight patients of the placebo group wished to take part in the CyA treatment procedure. The other two (patients 14 and 20) preferred to receive an alternative treatment. The mean percentage reduction in PASI of those who received CyA treatment (mean dose 5.7 mg/kg/d) was 90% after 4 weeks when compared with PASI at the and of 4 weeks on placebo (Table 5 and Fig 1B).

Adverse effects

In none of the patients was the CyA dose reduced because of clinical, haematologic, or biochemical side-effects. The clinical side-effects in the total of 18 patients receiving CyA were aching muscles (5), fatigue (2), headache (1), mild painful gynecomastia (one male), tremor (1), gastrointestinal upset (1), development of mild hypertrichosis (two males), and verruca vulgaris (1).

The increase of the systolic blood pressure in the first 4 weeks of CyA treatment (patients 1 to 10), compared to the value of the placebo patients in the same period (patients 11 to 20) was significant ($p = .03$), but such a significant difference could not be recorded for the diastolic blood pressure. The shift of the systolic blood pressure within the CyA-treated group of periods 0 to 4 weeks, 0 to 12 weeks, and 0 to 24 weeks was significant (SRT) with p values of .03, 0.3, and .05, respectively, whereas the diastolic blood pressure did not show significant differences (Table 6). The increase of the serum creatinine in phase 1 of CyA-treated patients compared to the change in creatinine of placebo patients was not significant ($p = .08$). The creatinine values at weeks 4 and 12

within the CyA group did not differ significantly. In period 0 to 24 weeks, on the other hand, the increase proved to be significant (p = .0.5, SRT) (Table 6). This was less than 40% above their respective individual baselines. In all patients the serum creatinine level rapidly returned to normal when the CyA dose was reduced (phase 2) or stopped.

Discussion

With CyA an almost complete remission of recalcitrant psoriasis was obtained within 4 weeks in 4 out of 18 patients (22%) with a low mean dose of 5.6 mg/kg/d, while in 15 (83%) an impressive amelioration (reduction in PASI of 75%) was seen (Table 7). These results of low-dose CyA are significantly better than placebo. In view of the relatively minimal side-effects, CyA represents an advance in the short-term treatment of psoriasis.

In general it can be concluded that the oral dose of CyA (mg/kg/d) is a more important hallmark for therapeutic results than the measurements of whole blood trough levels.

The difference observed in the improvement of the group that received CyA initially (mean percentage reduction in PASI score after 4 weeks 72%) and of the group that switched from placebo to CyA (mean percentage reduction in 4 weeks 90%) might be mainly explained by two reasons: the existence of a varying sensitivity of psoriasis to CyA in individual cases and the different character of that part of the study (open and out-clinic setting). In one patient (patient 6) there was a reduction in PASI of less than 50%. This patient, however, had an excellent response when the CyA dose was increased to 6 mg/kg/d.

The experiences in our center and of Ellis et al. [11], learn that low-dose CyA (5 mg/kg/d) has little or no effect in patients with active guttate psoriasis, especially when triggered by bacterial infections. A case of recalcitrant psoriasis pustulosa (Von Zumbusch type), which responded to a much higher dose of CyA, has also been published [14]. Additional conclusions can be drawn with regard to the efficacy of low-dose CyA. During the tapering off phase a further clinical improvement was seen at doses between 2 and 3 mg/kg/d. In a recent open trial [10], clearance of psoriasis was observed in a

period of 2 to 12 weeks (mean 7.4 weeks) at doses between 1 and 5 mg/kg/d (mean 3.3 mg/kg/d). These data and ours demonstrate that 3 mg/kg/d represents a critical effective CyA dose in certain sub-groups of patients with chronic plaque psoriasis.

In phase 3 of the trial it was difficult to maintain a treatment-free regimen. Three patients preferred additional treatment (drop-outs), because they had developed new lesions on hands and face. Four patients continued without CyA. Two of them had a relapse in week 16, another two in week 24. One patient (patient 1) remained symptom-free even 3 months after stopping CyA. It can thus be concluded that the relapse time differed very much among individuals (mean time to relapse 6.5 weeks) (see colour plate 3). This last patient (patient 1) had the habit, since his youth, to take fish oil daily. In itself this diet regimen may have an influence on psoriasis, as fish oil contains large amounts of arachidonic acid and also some eicosapentaenoic acid [15]. The intake of dietary polyunsaturated fatty acid may well potentiate the effect of CyA. This intriguing observation needs further investigation.

The side-effects that were observed were no reason to adjust the CyA dose. The diastolic blood pressure did not show a significant increase, neither within the CyA-treated group nor compared with the placebo group. The nonsignificant change in creatinine (in phase 1) may be caused by the small number of patients. The p value, however, points to a possible real difference. All the mild clinical and biochemical adverse reactions normalized during or shortly after phase 3.

The proven influence of CyA prompted to investigate the composition of the infiltrate in psoriasis skin more thoroughly. CyA may interfere with T cell functions, by interference with interleukins, in particular with interleukin-2 [16]. The striking response of severe psoriasis to low dosages of CyA could be considered a powerful argument for an essential role of T cells is psoriasis [17-19]. An additional immunological explanation for the effectiveness of CyA in psoriasis might be that the drug interferes with the antigen presenting capacity of dendritic cells [20,21], especially in view of the presence in vivo of relatively large numbers of dendritic cells bearing Langerhans cell and interdigitating cell immunophenotypes in psoriasis [19]. It has been reported that CyA does not inhibit

epidermal cell growth [22]. However, abnormal keratinocyte proliferation in psoriasis can be induced by epidermal growth stimulating factors liberated by inflammatory cells. This release might be inhibited indirectly by CyA due to its effects on T-cells [23,24]. Of interest are observations indicating that even after a short period, 3 to 7 days, of high-dose CyA treatment, the epidermal mitotic activity in psoriatic skin is decreased significantly [11]. This observation fits in with our finding that within 2 weeks of treatment with low-dose CyA, reductions in PASI score of 50% or more can be obtained.

We have suggested that low dose CyA might be of use in limited courses for the treatment of severe episodes of psoriasis ("crisis intervention") [8]. In that study, it was shown that slightly increased serum creatinine levels normalized again after withdrawal of CyA. However, additional monitoring of the glomerular filtration rate is needed in further prospective studies in larger groups of patients to arrive at an optimal regimen for CyA therapy in psoriasis. If we can limit serious side-effects, low-dose CyA therapy could have an important place in maintaining clearance of or improvement in severe psoriasis for longer periods.

Table 1. Background data of cyclosporin A and placebo patient groups as determined at the start of the study

Cyclosporin A

patient no.	trial no.	sex	age (year)	duration of disease (year)	weight (kg) week 0
1	2	male	65	16	66
2	4	male	62	43	64
3	5	male	42	17	59
4	6	female	67	11	77
5	9	male	63	54	71
6	21	male	58	50	59
7	22	female	62	21	93
8	25	male	30	11	86
9	26	male	30	13	64
10	30	male	67	36	63
N = 10	m/f ratio = 8/2		mv: 54.6	27.2	70.2

Placebo

patient no.	trial no.	sex	age (year)	duration of disease (year)	weight (kg) week 0
11	1	male	53	44	85
12	3	female	44	17	84
13	7	male	29	10	60
14	8	male	40	10	71
15	10	male	26	3	74
16	23	female	60	48	75
17	24	female	49	36	70
18	27	female	75	4	68
19	28	male	39	21	81
20	29	female	59	34	58
N = 10	m/f ratio = 5/5		mv: 45.6	22.7	72.6

m/f = male over female ratio
mv = mean value

Table 2. Tapering off schedule for the dosage of CyA (ml/d)* during week 5-12 of the trial varying dependant on the individual dose in ml/d at the end of week 4

Tapering off CyA (Phase 2)	Daily dosage of CyA (ml/d) at end week 4 (phase 1)		
	3	4	5
Dose of CyA in week 5 & 6	2	3	4
Dose of CyA in week 7 & 8	2	2	3
Dose of CyA in week 9 & 10	1	2	2
Dose of CyA in week 11 & 12	1	1	1

* 1 ml contains 100 mg CyA.

Table 3. Doses of cyclosporin A (mg/kg/d)* whole blood trough levels (ng/ml) in 10 patients with severe psoriasis**

	phase 1								phase 2							
week	1		2		3		4		5 and 6		7 and 8		9 and 10		11 and 12	
Patients	*	**	*	**	*	**	*	**	*	**	*	**	*	**	*	**
P 1	6.1	400	6.1	610	6.1	490	6.1	530	4.5	610	3	290	3	220	1.5	≤ 60
P 2	6.3	940	6.3	1060	5.6	750	5.6	250	4.7	700	3.1	590	3.1	250	1.5	260
P 3	5.1	230	6.8	290	6.8	400	6.8	670	5.1	1730	3.3	60	3.3	210	1.3	n.d.
P 4	5.2	710	5.2	460	5.2	480	5.2	410	3.9	350	2.6	130	2.6	80	1.3	< 60
P 5	5.6	430	5.6	430	5.6	310	5.6	350	4.2	350	2.8	180	2.8	180	1.4	90
P 6	5.1	539	5.1	584	5.1	347	5.1	702	***							
P 7	4.3	680	4.3	544	4.3	801	4.3	n.d.	4.3	751	3.2	862	2.1	60	1.1	< 60
P 8	5.8	907	5.8	824	5.8	1190	5.8	1020	4.7	778	3.5	n.d.	2.3	n.d.	1.2	< 60
P 9	6.3	451	6.3	450	6.3	867	6.3	n.d.	4.7	309	3.1	250	3.1	263	1.5	< 60
P 10	6.3	1085	4.8	567	4.8	n.d.	4.8	1720	4.7	n.d.	3.2	524	3.2	571	1.7	305
Mean values	5.6	637	5.6	582	5.6	596	5.6	562	4.5		3.1		2.8		1.4	

mean dose (for n = 10) = 5.6 mg/kg/d

mean dose (for n = 9) = ∾ 3 mg/kg/d

** Cyclosporin RIA-Kit (Sandoz Ltd, Basel, Switzerland)
CyA blood conc. 900 ng/ml were peak levels
n.d.: CyA blood conc. not measured

*** P 6 = non-responder (see Table 3 and text)

Table 4. Reduction in PASI in 10 patients with severe psoriasis treated with cyclosporin A (study phase 1-3)

Patients	PASI baseline	(study phase 1) end of week:				% reduction PASI to baseline	(study phase 2) end of week:				% reduction PASI to baseline	(study phase 3) end of week:		
(n = 10)	before start	1	2	3	4	4 wk	6	8	10	12	12 wk	16	20	24
P 1	29.7	24.5	16.2	7.2	6.0	80%	3.9	3.9	2.1	0.4	99%	2.1	2.1	2.1
P 2	34.0	17.9	12.1	10.9	12.2	64%	11.5	10.7	15.6	22.4[R]	34%	relapse in week 12		
P 3	42.8	37.3	12.8	11.0	9.9	77%	1.4	0.8	4.0	4.0	91%	8.3	13.1	27.1[R]
P 4	42.2	23.6	14.9	8.4	7.2	83%	5.2	3.0	7.8	6.8	84%	d.o.		
P 5	51.5	46.6	20.1	17.8	12.2	76%	2.4	4.0	6.0	6.0	88%	d.o.		
P 6	21.4	22.2	20.1	18.9	17.5	18%	*							
P 7	52.5	32.0	26.6	28.6	17.2	67%	7.8	7.2	9.0	15.4	71%	27.8[R]		
P 8	43.0	13.5	6.0	6.6	4.1	90%	1.9	n.d.	n.d.	1.5	97%	2.6	15.3	26.4[R]
P 9	19.6	18.2	10.0	4.3	4.0	80%	1.6	1.6	2.4	4.7	76%	16.5[R]		
P 10	28.4	30.4	14.6	6.1	5.8	80%	2.8	2.6	1.8	1.3	96%	d.o.		
Mean values	36.5	26.6	15.3	11.9	9.6	72%**				6.9	82%			
		mean values for n = 10							mean values for n = 9					

* : P6 = non-responder

** : Excluding patient 6, percentages reduction in the PASI to baseline is 79%

R : Relapse ≥ 50% of PASI baseline value

n.d. : PASI not performed

d.o. : drop out: patient unlikely to comply prescriptions

Table 5. Initial PASI scores and percentages reduction in PASI in 8 of 10 patients switching from placebo (weeks 1-4) to CyA treatment (weeks 1-4)

	Placebo: weeks 1-4			CyA: weeks 1-4 (mean dosage 5.7 mg/kg/d)		
Patients (n = 10)	PASI (baseline I)	% reduction PASI to baseline I	PASI end of week 4 (baseline II)	PASI end of week 4	% reduction PASI to baseline II	mean dosage (mg/kg/d)
P 11	50.2	11%	44.5	5.0	89%	5.9
P 12	26.2	21%	20.8	4.8	77%	6.0
P 13	26.1	− 7%	28.0	0	100%	5.7
P 14	21.8	28%	15.6	d.o.*		
P 15	22.0	−36%	30.0	0	100%	5.4
P 16	22.4	6%	21.0	3.0	86%	5.3
P 17	52.2	− 1%	52.7	1.8	97%	5.6
P 18	28.0	7%	26.0	1.6	94%	5.8
P 19	30.2	−12%	33.8	7.4	78%	6.2
P 20	21.2	14%	18.2	d.o.*		
Mean values	30.0	~ 3%	29.1	3.0	90%	5.7
	mean values for n = 10			mean values for n = 8		

* d.o. = drop outs (P 14 and P 20) were unlikely to comply further prescriptions

Table 6. Serum creatinine, min-max (mean), values in μmol/l during cyclosporin A (week 0-24) and placebo (week 1-4)

week	0	4	12	24
CyA	54- 97 (77.5)	70-94.0 (81.6)	66-96 (84.4)	69-94 (81.9)
Placebo	55-106 (80.0)	51-99.0 (77.8)		

Bloodpressure. Systolic and diastolic, min-max (mean), pressure values in mmHg during cyclosporin A (week 0-24) and placebo (week 1-4)

Systolic blood pressure

week	0	4	12	24
CyA	105-160 (130.5)	115-170 (143.9)	110-160 (143.8)	125-180 (152.9)
Placebo	120-150 (135.0)	100-155 (133.0)		

Diastolic blood pressure

week	0	4	12	24
CyA	70-90 (80.5)	65-105 (88.3)	70-95 (83.8)	80-110 (90)
Placebo	75-90 (82.0)	60-110 (82.5)		

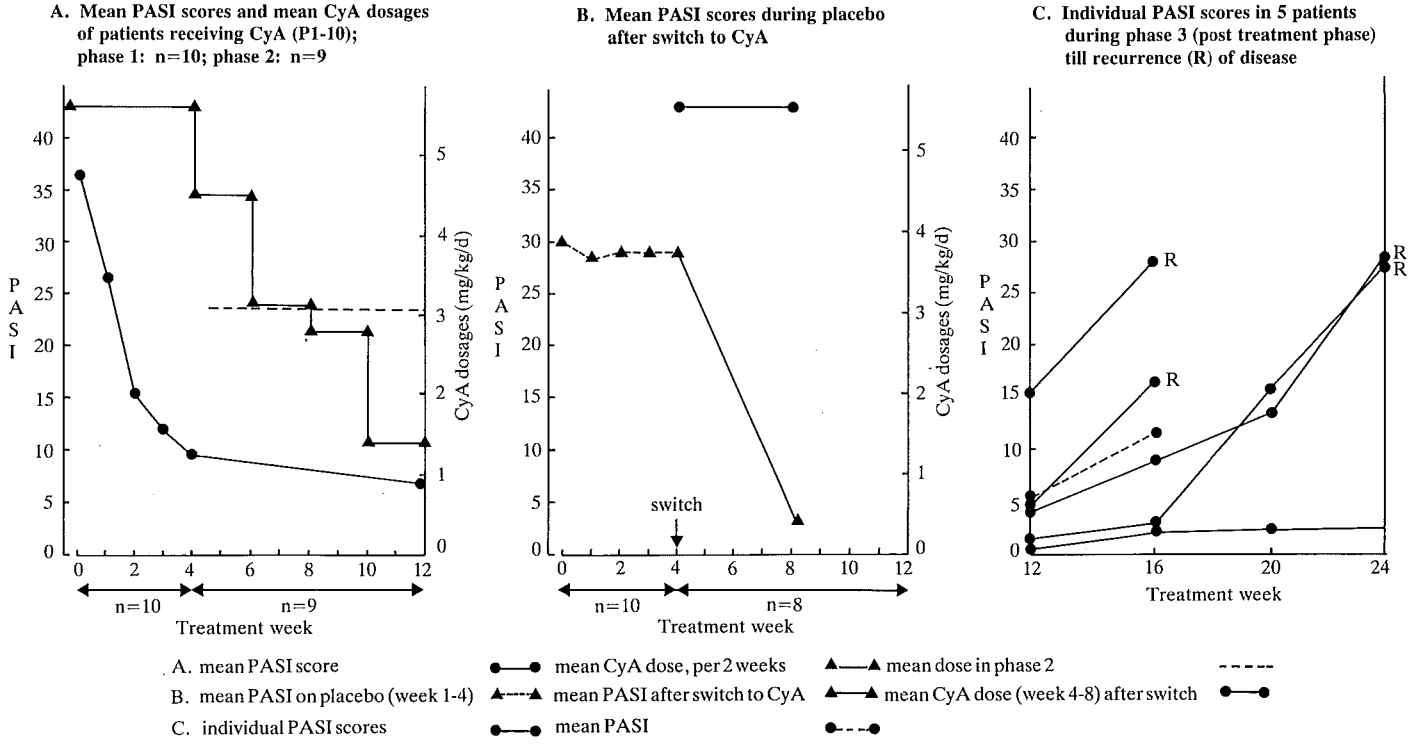
Table 7. Clinical response. I. In all CyA recipients (N=18) after treatment for 4 weeks. II. To CyA in patients (N=9) after the tapering off period (weeks 5-12)

	I	II
Clinical response based on the PASI reduction (%)	after 4 weeks CyA N = 18	after 12 weeks CyA N = 9
91-100 %	4 (22%)	4 (45%)
75- 90 %	11 (61%)	3 (33%)
51- 74 %	2 (11%)	1 (11%)
25- 50 %	1* (6%)	1** (11%)
0- 24 %	0 (0%)	0 (0%)
Total of patients	N = 18 (100%)	N = 9 (100%)
Mean dosage of CyA	week 1-4: 5.6 mg/kg/d	week 5-12: ∾ 3 mg/kg/d

* = P6, see text and Table 3

** = P2, see text and Table 3

Figure 1.


A. Mean PASI scores and mean CyA dosages of patients receiving CyA (P1-10); phase 1: n=10; phase 2: n=9
B. Mean PASI scores during placebo after switch to CyA
C. Individual PASI scores in 5 patients during phase 3 (post treatment phase) till recurrence (R) of disease
PASI
CyA dosages (mg/kg/d)
switch
n=10
n=9
n=8
Treatment week
R
A. mean PASI score
B. mean PASI on placebo (week 1-4)
C. individual PASI scores
mean CyA dose, per 2 weeks
mean PASI after switch to CyA
mean PASI
mean dose in phase 2
mean CyA dose (week 4-8) after switch

References

1. Bennett WM, Norman DJ. Action and toxicity of cyclosporin. Ann Rev Med 1986; 37: 215-24.
2. Hess AD, Colombani PM, Esa AH. Cyclosporine and immune response: Basic aspects. In: CRC Critical Reviews in Immunology. CRC Press Inc, 1986; 123-49.
3. Page EH, Wexler DM, Guenther LC. Cyclosporin A. J Am Acad Dermatol 1986; 14: 785-91.
4. Joost van Th, Stolz E, Heule F. Cyclosporin A and severe atopic dermatitis. Arch Dermatol 1987; 123: 166-76.
5. Mueller W, Herrmann B. Cyclosporin A for psoriasis. N Engl J Med 1979; 301: 555.
6. Harper JI, Keat ACS, Staughton RCD. Cyclosporin for psoriasis. Lancet 1984; ii: 981-2.
7. Van Hooff JP, Leunissen KML, van der Staak W. Cyclosporin for psoriasis. Lancet 1985; i: 335.
8. Van Joost Th, Heule F, Stolz E et al. Short-term use of cyclosporin A in severe psoriasis. Br J Dermatol 1986; 114: 615-20.
9. Griffiths CEM, Powles AV, Leonard JN et al. Clearance of psoriasis with low dose cyclosporin. Br Med J 1986; 291: 731-2.
10. Marks JM. Cyclosporin A treatment in severe psoriasis. Br J Dermatol 1986; 115: 745-746.
11. Ellis CN, Gorsulowsky DC, Hamilton TA et al. Cyclosporin improves psoriasis in a double-blind study. J Am Med Assoc 1986; 256: 3110-6.
12. Fredriksson T, Petterson V. Severe psoriasis; oral therapy with a new retinoid. Dermatologica 1978; 157: 238-44.
13. Palestine AG, Austin HA, Balow JE et al. Renal histopathologic alterations in patients treated with cyclosporine for uveitis. N Engl J Med 1986; 314: 1293-8.
14. Meinardi MMHM, Westerhof W, Bos JD. Generalized pustular psoriasis (Von Zumbusch) responding to cyclosporin A. Br J Dermatol 1987; 116: 269-70.
15. Kragballe K, Voorhees JJ. Arachidonic acid in psoriasis. Pathogenic role and

pharmacological regulation. Acta Derm-Venereol (Stockh) 1985; suppl 120: 12-7.

16. Bendtzen K. Ciclosporin (cyclosporin A): Prototype of a new generation of immunosuppressive drugs. Allergy 1984; 39: 565-71.

17. Bos JD, Hulsebosch HJ, Krieg SR et al. Immunocompetent cells in psoriasis. In situ immunophenotyping by monoclonal antibodies. Arch Dermatol Res 1983; 275: 181-9.

18. Baker BS, Swain AF, Valdimarsson H et al. T cell populations in the blood and skin of patients with psoriasis. Br J Dermatol 1984; 110: 37-44.

19. Bos JD, van Garderen ID, Krieg SR et al. Different in situ distribution patterns of dendritic cells having Langerhans (T6+) and interdigitating (RFD 1+) cell immuno-phenotype in psoriasis, atopic dermatitis and other inflammatory dermatoses. J Invest Dermatol 1986; 87: 59-61.

20. Varey AM, Champion Br, Cooke AK. Cyclosporine affects the function of antigen presenting cells. Immunology 1986; 57: 111-4.

21. Knight SC, Balfour B, O'Brien J et al. Sensitivity of veiled (dendritic) cells to cyclosporine. Transplantation 1986; 41: 96-100.

22. Kato N, Halprin KM, Taylor JR. Cyclosporin A does not inhibit epidermal cell growth at therapeutic levels. J Invest Dermatol 1987; 88: 52-54.

23. Kragballe K, Desjarlais L, Voorhees JJ. Leukotrienes [B_4] [C_4] and [D_4] stimulate DNA synthesis in cultured human epidermal keratinocytes. Br J Dermatol 1985; 113: 43-52.

24. Valdimarsson H, Baker BS, Jonsdottir J et al. Psoriasis: A disease of abnormal keratinocyte proliferation induced by T lymphocytes. Immunol Today 1986; 7: 256-9.

Chapter 5

Three long-term regimens with cyclosporin A for psoriasis vulgaris

This chapter is mainly based on the following manuscript:

Three long-term regimens with cyclosporin for psoriasis vulgaris.
Heule F, Bousema MT, Laeijendecker R, van Joost Th. Acta Derm Venereol (Stockh) 1989; 146: 171-5.

Summary

Nineteen patients with severe plaque type psoriasis were selected and divided in three groups to evaluate different long-term treatment programmes with cyclosporin A (CyA) (up to 130 weeks). Group 1 received a continuous treatment and group 2 an intermittent treatment on a low dose. The clinical results proved to be comparable, the side effects however were less. Group 3 received a combination of CyA and Tigason^{R}, but Tigason^{R} did not show an additional beneficial effect.

The continuous and intermittent, long-term regimes constitute a well-balanced approach for CyA treatment in psoriasis, next to the short-term treatment which we described before.

Introduction

Cyclosporin A (CyA, Sandimmune^{R}) is increasingly used to treat psoriasis vulgaris. In severe attacks and used for a short time (1-3 months) its therapeutic effect is clear [1,2,3]. In therapeutic doses the main side-effect, nephrotoxicity, seems to be reversible. However, psoriasis shows remissions and exacerbations that pose intricate questions regarding monitoring CyA during longer periods [4,5,6]. This study evaluates three different approaches with the aim to optimize drug effectiveness with minimal side effects over a longer period of time (mean time 58 weeks for 19 patients) than has hitherto been studied.

Patients en methods

From our earlier studies [1,2] with patients who had a chronic plaque form psoriasis of a severe character, 19 patients chose to go on with CyA treatment (Informed Consent was given). The selection criteria had been very strict (no pregnancy, renal or liver disease, uncontrolled infections, malabsorption syndrome and addiction to alcohol or drugs) and were revised for renal or liver disease and hypertension.

Besides psoriasis, the following concomitant diseases were present: ulcus duodeni (1), diabetes mellitus (2) and CARA (2). Three patients had a history of tuberculosis, now confirmed by X-ray to be silent. They all received isoniazide (INH) prophylaxis. Analgetics were allowed for severe (psoriatic) arthropathy.

The 19 patients were treated with CyA (at random by a blind investigator). In retrospect 2 main groups could be formed; Group 1 (n=9, see Table I) received a continuous treatment with CyA and group 2 (n=10, see Table I) received an intermittent treatment. When a dosage of 5 mg/kg/d was not able to suppress psoriatic disease below PASI level ≤ 5 in groups 1 or 2, in 50% of the episodes Tigason^R (etretinate, see Chapter 2) was added to the CyA prescription (group 3).

General procedure. The initial attack was treated with CyA to gain a remission. The severity of the skin disease was scored with the Psoriasis Area and Severity Index (PASI) (Addendum 1). The dosage used to induce a remission in about 5 weeks was 5 mg/kg/d in 2 equal oral doses of a solution containing 100 mg/ml CyA, with individual adjustments.

A remission (R) was defined as an improvement of the clinical state when PASI becomes equal to 5. This means an improvement of $\geq$ 80% in most cases. The period of time to reach this level is called the Remission Induction (RI) time. When the clinical conditions remained good (and PASI $\leq$ 50% of the initial value) a time lapse was passed which was called the maintenance (M) period.

When PASI reached a value over 50% of the initial value, an exacerbation (E) began. Each exacerbation was treated as in the initial period.

Procedure in group 1. The starting dose was diminished to the lowest possible level to maintain PASI $\leq$ 5. Dose adjustments were an increase of the dose when PASI $\geq$ 5 or when an exacerbation occurred. On the other hand, a decrease was effectuated when PASI $\leq$ 5 or when serious side effects took place.

Procedure in group 2. Conform group 1 a remission was induced. Then the CyA dosage was weaned off to zero and a CyA-free period followed. Only when the clinical situation aggravated and the E-point was passed, CyA was prescribed again. In this way each episode of activity was handled.

Procedure in group 3. In groups 1 and 2 six periods were treated with CyA in combination with Tigason^R (20-40 mg/d) to induce a remission. Anamnestic Tigason^R-

resistance was no reason to withhold this therapy.

Safety parameters and side effects. Serum creatinine over 130 μmol/l was considered to be a sign of nephrotoxicity. The upper limit of normal alkaline phosphatase was 75 U/l. Platelet counts that passed 320 x 10^9/l were considered as reactive. Hypertension was defined as a diastolic pressure over 95 mmHg. The patients were seen weekly in the out-clinic, in the first 3 months of the trial, later on once very month.

Results

Group 1. In this group 9 patients were treated during 19 episodes of active psoriasis: 16 on CyA only, 3 on CyA + Tigason^R (see group 3) (Tables II and IVa). In patients on CyA, 13 exacerbations were brought into a remission with very good result (PASI $\leq$ 5) in a mean time of 5.9 weeks with 5.2 mg/kg/d CyA. This resulted in a mean maintenance time of 24.3 weeks on 3.7 mg/kg/d (n=11). Three exacerbations (in 3 patients) did react with an effect < 65% on 5.8 mg/kg/d CyA in a mean time of 4.5 weeks.

Group 2. The 10 patients of this group got a treatment during 27 episodes: 24 on CyA only, 3 on CyA plus Tigason^R (see group 3) (Tables III and IVb). Of 24 episodes on CyA, 19 had a very good result (PASI $\leq$ 5) in a mean time of 5 weeks with 5.5 mg/kg/d CyA. The maintenance time had a weaning period of 6.9 weeks on 3.2 mg/kg/d and CyA could be stopped for 16.5 weeks until the E-point was passed. Five exacerbations showed an effect < 65% in 9 weeks on 4.7 mg/kg/d. When groups 1 and 2 were compared considering RI time and doses, there was no substantial difference. Maintenance times of group 1 and group 2 were 24.3 and 23.4 weeks, respectively, when weaning period and CyA-free period in group 2 were combined. These results were reached with comparable doses (Table IV). RI_1 , RI_2 and RI_3 are analyzed in groups 1 and 2 and in comparison showed that in the course of time slightly less CyA (25%) was used for the same clinical result. This, however, led to a longer RI time (60%).

Group 3. In this category 2 patients from group 1 (3 episodes) and 2 patients from group 2 (3 episodes) were treated on the combination therapy (Table IV a and b). The representatives of group 1 in group 3 showed a RI time that was twice as long as the part of group I that only got CyA at the same dose.

The representatives of group 2 in group 3 needed less CyA to clear the skin in a slightly

longer time than the part of group 2 that only got CyA. The small number of patients/episodes in this group only allows limited conclusions.

Reasons to change doses or stop CyA treatment in all groups were serious side-effects (creatinine rise, psychosis), drug interaction (Prolixan^R), active intercurrent disease (asthma bronchiale) or the patient's wish.

Hypertension was no direct reason to stop. An insufficient reaction to antihypertensive drugs was not seen. With the doses of CyA that were prescribed, not all arthropathy could be prevented casu quo cured. Several drugs were used for this aspect from different pharmacological groups. On these drugs no exceptional signs of nephrotoxicity were seen, with the exception of Prolixan^R (azapropazon, an NSAID). This parmacon was the "routine"-prescription of the consultant rheumatologist during the trial period.

Side-effects

During these long-term treatment programmes the well-known side effects were seen but also other complications were noticed, mostly with small frequencies (Table V). Any effect returning in another episode in a patient was counted as one.

Hypertension was seen in 47% of the patients (n=19). For 6 patients adequate treatment was started. In group 2 the blood pressure normalized and the antihypertensive drug could be stopped after the weaning phase.

A **rise of creatinine** was the second major side effect (42%). From these 8 patients 4 received Prolixan^R.

The exact reason for **weight** increase is unclear. Nephrotoxicity may be a cause of this effect.

Skin infections were not per se attributable to CyA treatment. Fatty ointments, being the basic skin care during this trial, might have facilitated bacterial phenomena.

Gynecomastia is an intriguing reaction as CyA is supposed to have an influence on the balance of peripheral androgen-estrogen ratio in male patients [7]. Careful screening with X-ray and biopsies did not reveal other pathology of breast tissue in these cases. The side effects in the 3 groups did not have the same frequency. Group 3 showed far fewer undesirable effects. In group 1, gastrointestinal problems and weight increase were four times more frequent than in group 2. The incidence of hypertension in group 2 was twice that in group 1.

Discussion

The doses needed to induce a remission in group 1 and group 2 ranged between 2.9 and 8.4 mg/kg/d (mean 5.4 mg/kg/d). The overall clinical effect of the treatment procedure in group 1 and group 2 seem to be the same: a beneficial effect on the skin in maintenance periods of 24.3 vs. 23.4 weeks (Table IV). The cumulative amount of CyA needed to reach this results, however, is less in group 2. Even more important is the fact that the negative effects (renal function deterioration and hypertension) can normalize in the CyA-free period.

Although there is a known interaction of CyA with many drugs [1,2], IHN was judged to be necessary to prevent reactivation of tuberculosis. This event did not happen in our patients.

Of the NSAID's that were taken during this trial, only Prolixan^R (azapropazon) had a demonstrable impact on the renal function. A synergistic effect on the other hand, might be due to fish oil in patient 13, as we suggested elsewhere [2]. The 2 patients with diabetes mellitus had a serious hypertension (up to 200/110 mmHg). The nephropathy is not comparable as one of these cases received Prolixan^R, but there might be a tendency to vasculopathic reactions. Although the epithelium of the airways in CARA patients is known to be colonized continuously with bacteria, and some consider this as a focus for psoriasis, we only treated asthmatic bronchitis with antibiotics and stopped CyA for a while. We got the impression that both (severe) diabetes and CARA were more difficult to maintain in a stable condition.

Group 1 and group 2 with CyA as monotreatment, compared to group 3 with combination therapy, showed more side effects. The clinical results of group 3 could be compared to "group 2 results $<$ 65%" (Table IVb).

All the side-effects that were seen tended to normalize after lowering CyA doses or disappeared after stopping the drug. In our opinion, the intermittent programme is superior. Main guidelines result from this study but an individual approach in monitoring CyA needs to be stressed.

Table 1. General data of patients in group 1 and 2, and duration of the CyA treatment

Group 1					Group 2				
Patient no.	Sex	BW (kg)*	Age (yrs)	CyA (wks)	Patient no.	Sex	BW (kg)	Age (yrs)	CyA (wks)
2	M	63	63	100	1	M	60	30	25
7	M	70	43	46	3	F	84	45	90
13	M	75	66	130	4	M	83	54	141
14	M	70	58	25	5	F	85	51	74
15	F	50	43	51	6	M	66	66	30
17	M	65	25	30	9	F	77	68	15
18	F	44	50	52	10	M	60	43	65
19	M	90	63	44	11	M	75	64	66
20	M	110	60	54	12	M	74	27	40
					16	F	69	39	24
N=9	M/F=7/2	71°	52°	59°	n=10	M/F=6/4	73°	49°	57°

* initial body weight (BW)

° mean values
group 1 + group 2:
mean BW: 72 kg
mean age: 50 yrs
M/F 13/6 or 68% and 32%
mean period of CyA treatment: 58 wks

Table 2. Remission induction and maintenance in group 1, continuous therapy over 1-4 exacerbations

Patient no.	IP[1]	RI_1[2]	dose[3]	M_1[4]	dose	RI_2	dose	M_2	dose	RI_3	dose	M_3	dose	RI_4	dose
2	34	5 p=10	6.2	5 p=10	4.4	4 p=10	4.8	50 p=10	3.3	16	3.8				
7	50	17	6.6T[5]	7.5	5.4	15 50%[7]	6T								
13	27	8	5.6	28	2.5	3	4	46	2.1	9	2.9	12	2.7	3	4T
14	58	5.5	5.6	19.5	4.9										
15	48	4.5	5.2	13	4.4	2 59%	6.8	–	–	2	6.2	7	4.2		
17	32	4.5	6.2	12.5	3.1	3 44%	5.7								
18	35	7.5	8.4	44.5	7.7										
19	25	2.5	5.2	4	3	2.5	3.3	33.5	2.8						
20	22	6.5	4.5	47.5	3.1										

Legends to Tables 2 and 3

1) IP = initial PASI; mean value in group 1 = 37; group 2 = 36.
2) RI = remission induction (wks) till PASI = 5, unless stated PASI (p) = 10.
3) dose in mg/kg body weight/day.
4) M = maintenance period, W = weaning phase, N = phase without CyA.
5) T = Tigason^R added (see text).
6) $\varnothing$ = weaning not to zero.
7) 50% means percentual reduction till lowest PASI.

Table 3. Remission induction and maintenance in group 2, intermittent therapy, over 1-4 exacerbations

Patient no.	IP[1]	RI_1[2]	dose[3]	M_1[4]	dose	RI_2	dose	M_2	dose	RI_3	dose	M_3	dose	RI_4	dose	M_4	dose
1	28	3.5	6.7	W 9.5 N 6.5	4.2T[5]	6	3.7T										
3	20	4	6.0	W 3.5 N 7	5.5	6 42% [7]	3.7	–	–	8	4.5	W 35Ø	3.1				
4	50	4	5.7	W 31 N 8	4.2	10 64%	5.7	–	–	20 57%	2.5T						
5	28	6	7.4	W 27Ø[6]	5.8	3	5.6			T only		–	–	8	2.5T	W 33Ø	0.8
6	30	3.5	5.8	W 12.5 N 42.5	4.5	10 64%	5.0	–	–	8.5	6.1						
9	42	6	4.7	W 6 N 16	2.3	3	7.1										
10	43	5	6.0	W 7 N 10	3.8	4 50%	6.7										
11	51	5.5	5.2	W 6.5 N 9	2.5	8	4.8	W 3Ø	3.6	7 41%	4.0			6	5.3		
12	30	3.5	5.4	W 16.5 N 22	2.8	2.5	4.1	W10.5Ø	4.3								
16	35	4.5	4.9	W 0 N 17.5	0	3.5	4.4	W 3.5 N 7.5	2.8T	6	3.6						

Table 4

a. Comparance of remission induction (RI)-time and maintenance periods (weeks) in group 1 and doses (mg/kg/d), mean values

Treatment	PASI reduction	RI-time	dose	episodes	Maint. time	dose	episodes
CyA	> 65%	5.9	5.2	13	24.3	3.7	13
	< 65%	4.5	5.8	3	–	–	–
CyA & Tigason^R	> 65%	10	5.3	2	7.5	5.4	1
	< 65%	15	6	1	–	–	–

b. Comparance of remission induction (RI)-time and maintenance periods (weeks) in group 2 and doses (mg/kg/d), mean values

Treatment	PASI reduction	RI-time	dose	episodes	Maint. time	dose	episodes
CyA	> 65%	5	5.5	19	weaning 6.9 no CyA 16.5	3.2	8
	< 65%	9	4.7	5	–	–	–
CyA & Tigason^R	> 65%	7	3.1	2	weaning* 33	0.8	1
	< 65%	20	1	1	–	–	–

* weaning not to zero

Table 5. Side-effects in groups 1 and 2 (n=19), group 3 (n=4)

		Group		
	N (%)	1	2	3
Serum creatinine > 130 µmol/l	8 (42)*	4	4	2
Alkaline phosphatase > 75 U/l	4 (21)	2	2	1
Platelets > 320 x 10^9/l	2 (11)		2	1
Hypertension, diastolic pressure > 95 mmHg	9 (49)	3	6	1
Weight increase > 5 kg	5 (26)	4	1	
Gastrointestinal complaints	5 (26)	4	1	
Hypertrichosis	3 (16)	1	2	1
Gynaecomastia (2 males, 1 female)	3 (16)	1	2	
Verrucae vulgaris	2 (11)	1	2	
Folliculitis, furunculosis, intertrigo	2 (11)		2	1
Paraesthesia	2 (11)	1	1	
Psychosis	1 (5)	1		
Orchitis	1 (5)		1	
Conjunctivitis	1 (5)	1		

* Prolixan^R-related creatinine rise in 4 of these patients.

References

1. Van Joost Th, Heule F, Stolz E et al. Short term use of cyclosporin A in severe psoriasis. Br J Dermatol 1986; 11: 615-20.
2. Heule F, Meinardi MMHM, van Joost Th et al. Low-dose cyclosporin effective in severe psoriasis. A double-blind study. Transplant Proc vol. XX, no. 3, suppl. 4 (June) 1988: 32-41.
3. Van Joost Th, Heule F, Bos JD. Eds. Cyclosporin (Sandimmune^{R}) in psoriasis. Actua Sandoz, nr. 13. Samson Stafleu, Alphen aan den Rijn/Brussel, 1988.
4. Meinardi MMHM, Bos JD. Cyclosporin maintenance therapy in psoriasis. Transplant Proc vol. XX, no. 3, suppl. 4 (June) 1988; 42-9.
5. Griffiths CEM, Powles AV, McFadden et al. Long-term cyclosporin for psoriasis. Br J Dermatol 1989; 2: 253-60.
6. De Rie MA, Meinardi MMHM, Bos JD. Analysis of side effects of medium-and low-dose cyclosporin maintenance therapy in psoriasis. Br J Dermatol 1990; 123: 347-53.
7. European multicenter trial group. Cyclosporin A as a sole immunosuppressive agent in recipients of kidney allografts from cadaver to donor. Lancet 1982; ii: 57-60.

Chapter 6

Topical cyclosporin A treatment in psoriasis and other dermatological diseases

Theoretical and practical aspects

This chapter includes the following manuscript:

Placebo-controlled study of psoriasis patients treated topically with a 10% cyclosporine gel.

Bousema MT, Tank B, Heule F, Naafs B, Stolz E, van Joost Th. J Am Acad Dermatol 1990; 22: 126-7.

This chapter is submitted for publication, 1991

Summary

The immunosuppressive properties of cyclosporin A (CyA) after systemic (oral) administration are now well documented in several dermatological disorders, especially in psoriasis. However, long-term oral use, even at low doses, is hampered by renal side-effects.

From a theoretical point of view in skin diseases there is an opportunity to bypass the oral route and administer CyA directly to the affected areas. The data of the experimental studies to date in psoriasis, alopecia, contact and atopic dermatitis as well as oral lichen planus and keloid scars are summarized and own experiences have also been presented. Theoretical considerations on the pharmacokinetics of CyA for topical application are also discussed.

Introduction

Cyclosporin A (CyA) has been used for the past ten years to treat a range of skin diseases with an acknowledged immunological background. The oral formulation of CyA (drink solution or soft gelatine capsules both containing 100 mg cyclosporin A per ml) used in short- and long-term treatment has side-effects that are now best evaluated in psoriasis. Among these, adverse effects on the kidney and hypertension are the most frequent. Other objective and subjective adverse effects were also recently reported [1]. The exact mechanism of action of CyA is not yet fully known but there is strong evidence that immunosuppression is induced via an antiproliferate effect on CD4+ helper T-lymphocyte subsets. A simultaneous inhibition of keratinocyte proliferation was also suggested [2]. Recent data also strongly indicate that CyA inhibits delayed type hypersensitivity. This may be partly due to impaired function of antigen presenting Langerhans cells [3]. Other targets for the biological activity of CyA may be inflammatory cells like neutrophils and the vascular endothelial cells. Whether such effects in human skin in vivo can be induced by circulating CyA or can also be induced by the drug administered topically (with or without a circulating fraction) is not yet clear [4]. Another route than the oral administration has many advantages if topical formulations of CyA are therapeutically

effective, without showing the side-effects.

Although a definite proof of local action of CyA cannot be given as yet, intra-epithelial accumulation and effects may be postulated from several studies. It is known from post-mortem studies in transplant patients that CyA in fact has an affinity for skin tissue [5]. Investigation of suction blister fluid from patients with psoriasis who were treated with a mean oral dose of CyA of 3.9 mg/kg/d and who were in a steady state showed a blister fluid concentration (BFC) of between 20-113 ng/ml while the whole blood through levels ranged from 236-935 ng/ml. The BFC was approximately 1/10th of the blood levels [6]. Intralesional injections with CyA result only in trace blood levels but produced a significant resolution in psoriatic plaques [7].
In this chapter, a summary of clinical trials with topical CyA in plaque psoriasis, psoriasis of the nails, alopecia, allergic contact dermatitis, oral lichen planus and keloid scars together with our own observations in these diseases is presented.

Clinical experiences

Psoriasis

Topical CyA showed an inhibitory effect on psoriasis-like inflammation in mice. Fisher et al [8] studied this phenomenon in the tumor-promoting phorbol ester (TPA)-induced inflammatory response in mouse skin. There was a decrease in cell infiltrate, epidermal thickness, ornithine decarboxylase (ODC) activity, ODC-mRNA accumulation and prostaglandin E_2 content. Protein kinase C, however, appeared not to be inhibited.

The clinical studies with topical CyA treatment in chronic, plaque-type psoriasis were performed with 2, 5 and 10% CyA in a range of vehicles, containing several of the additives shown in the Table, some under polyethylene occlusion [11-17]. At our centre 9 patients with psoriasis were enrolled in a double-blind, randomised study to compare a gel containing 10% CyA, 43% olive oil, 10% ethanol, 30% peglicol 5 oleate (Labrafil) and 7% colloidal silicium oxide (Aerosil) with an identical placebo gel without CyA. On 2 symmetric psoriatic plaques 0.3 ml of either gel was applied twice daily for 4 weeks. As

a result a total amount of 2352 mg CyA was applied to one lesion. No significant clinical difference was noticed between the CyA treated and the placebo treated lesions [17].
Also in other reported studies no therapeutic effect on the psoriatic plaques was observed using objective and subjective criteria, though some noticed a decrease in the number of neutrophils [14,16]. Blood samples taken to determine blood concentrations during the treatment showed inconsistent levels in a range that appeared to be too low to be therapeutically effective. In these trials no local or systemic side-effects were noticed. The barrier of the thick hyperkeratotic epidermal layers in psoriatic skin may be one of the causes for the lack of effectiveness.

In nail psoriasis, Tosti et al. [18] mentioned a fair response of topical CyA in 4 months. These observations have, however, not yet been confirmed.

Intralesional (injected or infused) CyA seems to be more effective [7,19-23]. The psoriatic skin tended to normalize in 5 days and in 4 weeks a significant resolution of lesions was observed in all cases. After 4 weeks a normal orthokeratotic pattern returned and epidermal and dermal accumulation of immunocompetent cells was decreased [20,23]. The blood levels were below sensitivity levels of HPLC and polyclonal RIA. Pain at the injection site and a cellulitis-like reaction were the major side-effects [20].

Alopecia areata and alopecia androgenetica

More or less severe hypertrichosis, both in male and female patients [colour plate 5 and 6], is reported as a side-effect of oral CyA in clinical trials by several authors (see Chapter 1). An effect on the androgen production seems not of a major importance as women show no virilization and some of the skin sites such as the earlobes and the nose that are involved are non-androgen dependent.
CyA induces the appearance of large follicles that produce thick hair stems besides vellus hairs turn into terminal hairs. After withdrawal of CyA the new hairs fell out quickly.

Both male pattern baldness or androgenetic alopecia which is a testosterone induced disease with an involution of anagen to catagen hair or even dysplastic hair roots and

alopecia areata which is a condition that shows an involution of the hair follicle and hair loss and is marked by a perifollicular infiltrate of T-lymphocytes have been treated locally with CyA [2,25-32].

In a two-months experiment in a 45 year old man with a longstanding androgenetic alopecia totalis who was treated with 5% CyA-cream (as oral suspension in cremor lanette FNA), double-blind, vehicle controlled, no substantial regrowth of hair was observed (own unpublished observations, 1985).
Gilhar et al. [30] evaluated topical CyA in a 4 month, double-blind study in male pattern alopecia. Significant regrowth was seen in 2 out of 8 patients but only in one hairgrowth was cosmetically satisfactory. A few sera in this trial showed trace amounts of CyA.
Parodi and Rebora used only 0.25% CyA in an alcohol/propylene glycol-containing medium to treat a patient with alopecia areata. This treatment resulted in complete hair regrowth after 16 months [27].

Though the results of the oral treatment with CyA seem promising in alopecia variants [1] the local application has not yet resulted in a reproducible, satisfactory response.

Contact dermatitis

In contact allergy a T-cell-mediated response is provoked by an allergen resulting in clinical dermatitis. The initial investigations with CyA to evaluate the cell-mediated immune response was quantified as immune delayed-type hypersensitivity (DTH) reaction by measuring the suppression of the oxazolone induced skin reaction in mice [33]. In animals [34-39] and in man [32,40,41] a decrease in DTH in the skin was noticed after topical application of CyA containing formulations. The mechanism of action may be a sufficient inhibition of the function of Langerhans cells present in the epidermis to suppress activation of T-lymphocytes.
Aldridge et al. [34] found a beneficial effect of 1-2% CyA in ethanol/olive oil 1 : 2 on dinitrofluorobenzene (DNFB)-induced contact allergy in guinea-pigs. CyA blood levels were lower than 50 ng/ml and they recorded no systemic side-effects.

Duncan et al [9] found that a DTH reaction to DNFB in guinea-pigs could be suppressed by a topical CyA formulation containing Azone and propylene glycol. Both the erythema response and the T-cell infiltrates were reduced on the test-sites on a 0.25, 0.5 and 5% CyA concentration compared to the vehicle treated sites.

Our own unpublished observations in two patients are as follows.
An adult male patient presented with a dermatitis due to wool alcohol. The allergen (wool alcohol) in combination with 5% CyA and the allergen without CyA were tested epicutaneously according to standardized test procedures. After 48 hours, the test site with CyA showed a reduction in response of about 50% as compared with the site without CyA.
A 45-year-old woman with longstanding psoriasis who suffered from hand-involvement was treated with systemic CyA. Her skin became quiescent. To exclude triggering contact factors (Koebner phenomenon) patch-tests were performed, but all tests were negative under CyA treatment. However, once the dose of CyA was decreased and then withdrawn, the eruption on the hands became worse upon contact with rubber household gloves. Skin-tests were performed again (3 months after stopping CyA) and strong positive reactions to rubber constituents and to her own gloves were observed. The DTH reaction in this case was hidden in the psoriasiform Koebner reaction due to the inhibitory effect of oral CyA.

Atopic dermatitis

Atopic dermatitis presents with an array of skin signs such as pruritis, redness, vesicles, oozing, urticarial swelling, dryness, scaling and lichenification often with a seasonal periodicity.
These can be explained mainly on the basis of both IgE-mediated humoral and cell-mediated immune mechanisms. In many patients immediate-type allergies can be detected for aero-allergens (pollens, house dust mite, human and animal dander). Systemic treatment with CyA was shown to have a beneficial effect in atopic dermatitis, especially the pruritis responded well [42], suggesting that the production and/or liberation of certain cytokines responsible for the pruritis were affected in rather short time. We

observed no effect on the serum IgE levels and this was confirmed by others [43]. The prick-test responses to aero-allergens were also unaffected by CyA [43]. This may emphasize the role of T-cell mechanisms in atopic disease.
De Prost et al [44] compared a gel containing 10% CyA with placebo in atopic dermatitis during 2 weeks. The improvement in pruritis, erythema, oozing, crusts, xerosis and lichenification was significantly superior at the sites treated with CyA than at the sites treated with placebo. No complete cures were observed. Blood CyA levels were always below the limit of detection. No systemic reactions were observed but irritation of the excipient (its alcoholic component?) was a major problem.

Oral lichen planus

The painful, debilitating erosive lichen of the oral cavity is histologically characterized by a heavy bandlike lymphocytic infiltrate consisting of the T-helper/inducer subtype at the dermal/epidermal junction. The epidermis shows increased numbers of T6-HLA-DR+ Langerhans cells but rarely dendritic cells. The surface of the keratinocytes also express HLA-DR antigen and intercellular adhesion molecule-1 (ICAM-1). Oral CyA treatment of cutaneous lichen planus reduced the lymphocytic infiltrate by 20% after 8 weeks and expression of ICAM-1 was no longer observed [50].

Several clinical studies with CyA in some form of a mouth wash [45-54] with daily amounts ranging from 1 [45] to 5 [48] ml CyA solution containing 100 mg/ml showed a very good response after 2 months. No systemic or local side-effects were noticed even though gum hyperplasia was reported after systemic therapy [colour plate 4]. The oily solution only left a waxy debris in many patients.
Analysis of the CyA content in the buccal mucosa revealed quantities that equalled those after systemic use [50]. The lack of cornified layers resulting in a better penetration of CyA could explain the therapeutic effect in this disease of the oral mucosa. Incidental reports on the swish and spit method in other mucosal diseases like bullous pemphigoid, cicatricial pemphigoid, pemphigus vulgaris and aphtous stomatitis do not allow firm conclusions yet [51,52].

Keloid scars

Hypertrophic scars can appear in the presternal area, over the deltoid region and on the earlobes. Apart from an increased collagen deposition by fibroblasts a perivascular T-cell infiltrate is thought to be relevant. The topical application of CyA resulted in a decreased T-cell infiltrate but did not alter the clinical picture [53].

Conclusions

Oral CyA has proved to be effective in a range of dermatological diseases with a suspected cell-mediated immunological involvement.
Topical application to the human skin, however, did not show the expected response in many studies. Newer approaches with intralesional administration and the swish and spit method for oral mucosal diseases seem more beneficial and indeed prove the local action of the drug.

The main explanations for the lack of effect of topical therapy can be summarized as follows. From a logistic point of view the principal barrier of the skin is the stratum corneum, this is especially true in psoriasis. CyA has a chemical structure with a relatively high molecular weight of 1.2 kD without an ionic polarization and it has a cyclic configuration. This combination of factors is a disadvantage for penetration although its lipophilic nature is an advantage. A poor penetration results in minimal absorption into the circulation. However a circulating fraction of CyA might not be necessary for the local action. A low local concentration that is insufficient to produce any therapeutic effect may also ensue from a quick absorption into the circulation (washout phenomenon). Absorbed and circulating CyA is metabolized in the liver and active metabolites on one hand may be responsible for the effects in the skin. Whether a proper metabolization in the skin per se takes place is still under investigation [55]. A high local turnover to inactive metabolites on the other hand may render it ineffective. The effectiveness of CyA metabolites is under investigation to obtain a precise image of structure-activity relationships but much more remains to be done. When CyA binds to elements in the skin for instance cell membranes of erythrocytes or keratinocytes and

lipoproteins it may not reach target cells like Langerhans cells or T-lymphocytes.
Among all these penetration through the stratum corneum seems a manageable factor. The solubility and the concentration of CyA in the formulation is important and so is its ability to redissolve for the duration of application. By increasing the hydration state and lipid fluidity of the stratum corneum the penetration may be increased. A list of substances with such qualities (enhancers) is shown in the Table. The study by Duncan et al [8] requires special attention. They demonstrated that the addition of penetration enhancers resulted in therapeutic effects of CyA doses which were otherwise ineffective.

Further pharmacokinetic studies in vitro with skin slice models, skin homogenates and skin perfusion models, the in vivo application of radiolabelled substances in animal and man [56] are necessary to explore newer topical formulations with increased penetration. Such formulations would allow the effective therapeutic treatment of skin diseases without the adverse effects of the drug.

Table

Penetration enhancers [8,9]

Salicylic acid
Urea
DMSO (dimethylsulphoxide)
Liposomes
Azone (1-dodecylazacycloheptan-2-one)
Tween 80 (sorbitan mono-oleate)
Labrafil (peglicol 5 oleate)
Propylene glycol
Ethanol
Imvitor (monoglyceride of caprilic acid)
Pyrrolidones

References

1. Mahrle G, Schulze HJ. Cyclosprin A - Dermatologische Indikation. Zeitschr Hautkr 1990; 65: 28-39.
2. Kanitakis J, Thivolet J. Cyclosporine. An immunosuppressant affecting epithelial cell proliferation. Arch Dermatol 1990; 126: 369-75.
3. Theunissen MBM, de Jager MH, Kapsenberg ML et al. Inhibitory effect of cyclosporine A on antigen and alloantigen presenting capacity of human epidermal Langerhans cells. J Invest Dermatol 1989; 93: 310.
4. Black KS, Nguyen DK, Protor CM et al. Site-specific suppression of cell-mediated immunity by cyclosporine. J Invest Dermatol 1990; 94: 644-8.
5. Ried M, Gibbons S, Kwok D et al. Cyclosporine levels in human tissues of patients treated for one week to one year. Transplant Proc 1983; 15: 2434-7.
6. Meinardi MMHM, van Eendenburg JP, Oosting J et al. Cyclosporin A levels in suction- blister fluid of patients with psoriasis treated systemically. Br J Dermatol 1990; 122: 671-6.
7. Hermann RC, Taylor RS, Ellis CN et al. Topical cyclosporine A for psoriasis: in vitro and clinical study of percutaneous absorption. Skin Pharmacol 1988; 1: 246-9.
8. Fisher GJ, Gupta AK, Duell EA et al. Cyclosporine A inhibits TPA-induced inflammatory hyperplastic response in mouse skin. J Invest Dermatol 1988; 90: 559.
9. Duncan JI, Payne SNL, Winfield AJ et al. Enhanced percutaneous absobtion of a novel cyclosporin A formulation and assessment of its immunosuppressive activity. Br J Dermatol 1990; 123: 631-40.
10. Cavanak T, Sucker H. Formulation of dosage forms. Progr Allergy 1986; 38: 65-72.
11. Schauder CS, Gorsulowsky DC. Topical cyclosporine A in the treatment of psoriasis. Clin Res 1986; 34: 1007a.
12. Griffiths CEM, Powles AV, Baker BS et al. Topical cyclosporin and psoriasis. Lancet 1987; i: 806.
13. Gilhar A, Winterstein G, Golan DT. Topical cyclosporin in psoriasis. J Am Acad

Dermatol 1988; 18: 378-9.

14. Schulze HJ, Mahrle G, Steigleder GK. Topical application of ciclosporin in psoriasis. In: Actua Sandoz 1988; 13: 102-4. Eds van Joost Th, Heule F, Bos JD. Stafleu Wetenschappelijke Uitgeversmij. Alphen a/d Rijn, The Netherlands.
15. Bunse T, Schulze HJ, Mahrle G. Locale Anwendung von Cyclosporin bei Psoriasis vulgaris. Z Hautkr 1990; 65: 538, 541-2.
16. Schulze HJ, Mahrle G, Steigleder GK. Topical cyclosporin A in psoriasis. Br J Dermatol 1990; 122: 113-4.
17. Bousema MT, Tank B, Heule F et al. Placebo-controlled study of psoriasis patients treated topically with a 10% cyclosporine gel. J Am Acad Dermatol 1990; 22: 126-7.
18. Tosti A, Guerra L, Bardazzi F et al. Topical ciclosporin in nail psoriasis. Dermatologica (Basel) 1990; 180: 110.
19. Wilkinson DI, Farber EM, Cohen EN et al. Psoriasis improves with infusion of microgram amounts of cyclosporine A into lesions. J Invest Dermatol 1990; 94: 591.
20. Ho VC, Griffiths CEM, Ellis CN et al. Intralesional cyclosporine in the treatment of psoriasis: a clinical, immunological and pharmacological study. J Am Acad Dermatol 1990; 22: 94-100.
21. Powles AV, Baker BS, Mc Fadden J et al. Intralesional injection of cyclosporine in psoriasis. Lancet 1988; i: 537.
22. Ho VC, Griffiths CEM, Ellis CN et al. Intralesional cyclosporine A in the treatment of psoriasis: a clinical, immunologic and pharmacokinetic study. Clin Res 1989; 37: 659a.
23. Baker BS, Powles AV, Savage CR et al. Intralesional cyclosporin in psoriasis: effects on T-lymphocyte cell and dendritic subpopulations. Br J Dermatol 1989; 120: 207-13.
24. Powles AV, Baker BS, McFadden JP et al. Intralesional cyclosporin in psoriasis. Acta Derm Venereol (Stockh) 1989; 146: 148-50.
25. Biren CA, Barr RJ. Dermatological applications of cyclosporine. Arch Dermatol 1986; 122: 1028-32.
26. De Prost Y, Teillac D, Paquez F et al. Placebo-controlled trial of topical

cyclosporine in severe alopecia areata. Lancet 86; ii: 803-4.

27. Parodi A, Rebora A. Topical cyclosporine in alopecia areata. Arch Dermatol 1987; 123: 165-6.

28. Pigatto PD, Montalbano MM, Cirillo R et al. Low concentration of topical cyclosporin A for severe alopecia. Ann Ital Clin Sper 1988; 42: 377-82.

29. Gilhar A, Pillar T, Etzioni A. Topical cyclosporine A in alopecia areata. Acta Derm Venereol (Stockh) 1989; 69: 252-3.

30. Gilhar A, Pillar T, Etzioni A. Topical cyclosporine in male pattern alopecia. J Am Acad Dermatol 1989; 22: 251-3.

31. Coulson IH, Holden CA. Topical cyclosporin A in alopecia totalis: Failure of therapeutic effect due to lack of penetration. Br J Dermatol 1989; 121, suppl 34: 53-4.

32. Thomson AW, Aldridge RD, Sewell HF. Topical cyclosporine in alopecia areata and nickel contact dermatitis. Lancet 1986; ii: 971-2.

33. Wenger RM. Synthesis of cyclosporin and analogues: structural and conformational requirements for immunosuppressive activity. Prog Allergy 1986; 38: 46-64.

34. Aldridge RD, Thomson AW, Rankin R et al. Inhibition of contact sensitivity reactions to DNFB by topical cyclosporine application in the guinea pig. Clin Exp Immunol 1985; 59: 23-8.

35. Nakagawa S, Oka D, Jinno Y et al. Topical application of cyclosporine on guinea pig allergic contact dermatitis. Arch Derm 1988; 124: 907-10.

36. Lembo G, Balato N, Patruno C et al. Topical application of cyclosporine on guinea pig allergic contact dermatitis. Arch Derm 1989; 125: 1431-2.

37. Lembo G, Balato N, Patruno C et al. Influence of topical cyclosporin A on patch test reactions. Contact Dermatitis 1989; 20: 155-6.

38. Cole GW, Shimomaye S. Goodman M. The effect of topical cyclosporin A on the elicitation phase of allergic contact dermatitis. Contact Dermatitis 1988; 19: 129-32.

39. Biren CA, Barr RJ, Ganderup GS et al. Topical cyclosporine: effects on allergic contact dermatitis in guinea pigs. Contact Dermatitis 1989; 20: 10-6.

40. Aldridge RD, Sewell HF, King G et al. Topical cyclosporine in nickel contact

hypersensitivity: results of a preliminary clinical and immunohistochemical investigation. Clin Exp Immunol 1986; 66: 582.

41. Reitamo S, Käyhkö K, Lauerma AJ et al. Topical cyclosporine and contact dermatitis in guinea pig and man. Arch Dermatol 1989; 125: 568.

42. Van Joost Th, Stolz E, Heule F. Efficacy of low-dose cyclosporine in severe atopic skin disease. Arch Dermatol 1987; 123: 166-7.

43. Munro CS, Higgins EM, Marks JM et al. Cyclosporin A in atopic dermatitis: therapeutic response is dissociated from effects on allergic reactions. Br J Dermatol 1991; 124: 43-8.

44. De Prost Y, Bodemer C, Teillac D. Randomised double-blind placebo-controlled trial of local cyclosporin in atopic dermatitis. Acta Derm Venereol (Stockh) 1989; suppl 144: 136-8.

45. Francès C, Boisnic S, Etienne S et al. Effect of the local application of ciclosporine A on chronic erosive lichen planus of the oral cavity. Dermatologica 1988; 177: 194-5.

46. Grattan CEH, Boon AP, Gregory J. A preliminary open study of topical cyclosporin for hypertrophic lichen planus. J Dermatol Treat 1989; 1: 39-41.

47. Balato N, de Rosa S, Bordonne F et al. Lichen erosivo; trattamento con ciclosporina A per uso topico. Ann Ital Derm Clin Sper 1989; 43: 141-4.

48. Eisen D, Griffiths CEM, Ellis CN et al. Cyclosporine wash and spit improves oral lichen planus in a double-blind study. J Invest Dermatol 1990; 94: 520.

49. Eisen D, Griffiths CEM, Ellis CN et al. Cyclosporin wash for lichen planus. Lancet 1990; 335: 535-6.

50. Eisen D, Ellis CN, Duell E et al. Effect of topical cyclosporine rinse on oral lichen planus: a double-blind analysis. N Eng J Med 1990; 323: 290-4.

51. Eisen D, Ellis CN. Topical cyclosporine for mucosal disorders. J Am Acad Dermatol 1990; 23: 1259-64.

52. Eisen D, Ellis CN, Voorhees JJ. Topical cyclosporin for oral bullous disorders. J Am Acad Dermatol 1990; 23: 936-7.

53. Duncan JI, Thomson AW, Muir IFK. Topical cyclosporin and T-lymphocytes in keloid scars. Br J Dermatol 1991; 124: 1090.

54. Balato N, de Rosa S, Bordonne F et al. Dermatological application of

cyclosporine. Arch Dermatol 1989; 125: 1430-1.

55. Duell E, Fisher V, Fisher G et al. Cytochrome P-450 metabolism of cyclosporine A by microsomes isolated from psoriatic epidermis, rat epidermis and rat liver. J Invest Dermatol 1990; 94: 519.

56. Behrendt H, Korting HC, Braun-Falco D. Zum Metabolismus von Pharmaka in der Haut. Hautarzt 1989; 40: 8-13.

Chapter 7

Efficacy of low-dose cyclosporin A and renal function monitoring in patients with severe recalcitrant psoriasis vulgaris

This chapter is based on the following manuscript:

Efficacy and safety of low-dose cyclosporin A in severe recalcitrant chronic plaque form psoriasis.

F. Heule, G.J. Wenting, R.M.L. Brouwer and Th. van Joost.

For the Dutch Psoriasis Study Group**. Submitted for publication 1991.

**Participating centers and physicians of the Dutch Psoriasis Study Group:

- Rotterdam, Departments of Dermato-Venereology and Internal Medicine I[1], University Hospital Rotterdam Dijkzigt: F. Heule, G.J. Wenting[1], R.M.L. Brouwer[1], Th. van Joost, M.T. Bousema, R. Laeijendecker, F.H.M. Derkx[1].
- Amsterdam, Departments of Dermatology and Internal Medicine[1], Free University Hospital: Th.M. Starink, T.J. Stoof, H.J.G. Bilo[1], A.J.M. Donker[1].
- Maastricht, Department of Dermatology, University Hospital St. Annadal: R.F.H.J. Hulsmans, M. Korstanje.
- Helmond, Department of Dermatology, St. Lambertus Hospital: H.A.M. Neumann, M.J. van der Broek.
- Heerlen, Department of Dermatology, De Wever Hospital: M.J.Th.Go, J.C.C.A. Lambers, J. Wuite.
- The Hague, Department of Dermatology, Leyenburg Hospital: H.J. van der Rhee.

Summary

The efficacy of cyclosporin A (CyA) in severe psoriasis is well established. However, there is genuine concern regarding the safety of long-term treatment with CyA. To date proper assessment of the extent of CyA-induced renal damage has been hampered by the crudeness of serum creatinine as a parameter to estimate glomerular filtration rate (GFR). The objectives of this study are a prospective evaluation of renal function at two doses of CyA with special emphasis on 1 - lowest effective dose, 2 - reliability of serial serum creatinine measurements to monitor changes in GFR and 3 - complete reversibility of renal dysfunction after stopping CyA.

This study is designed as a prospective, open, randomized multi-center trial in parallel groups in which the efficacy of 2.5 or 5.0 mg of CyA per kg/d is compared. Induction period: 3 months. Maintenance and tapering-off period: maximum 16 months. Post-treatment period: 3 months. After four weeks, the 2.5 mg dose may be adjusted to improve efficacy, the 5.0 mg dose may be reduced for safety reasons.

Six departments of dermatology in the Netherlands were involved in this study.

Seventy-four patients with severe plaque-type psoriasis were included. The results can be summarized as follows:

The speed, magnitude and duration of improvement appeared to be dose-dependent, the 5.0 mg dose being the more effective. However, when the resolution of the lesions of the skin is relatively unimportant, 2.5 mg/kg/d was a good starting dose since minimal side-effects were observed. In the patients treated with 5.0 mg/kg/d, 22% required dose adjustments for safety reasons (increase in serum creatinine $\geq$ 30% of the base line). At the end of the induction period the GFR in 44 patients decreased by 15% on the average ($p < 0.01$). In the range of GFR observed (mean 115 ml/min, range 51 to 216) serum creatinine appeared to be a poor predictor of changes in GFR. The effective renal plasma flow (ERPF) decreased by 16% on the average ($n=27$, $p < 0.01$). Prolonged treatment with CyA during the maintenance phase did not lead to a further reduction in the GFR and ERPF. After stopping CyA, serum creatinine returned to baseline values. In contrast, GFR and ERPF remained significantly below pretreatment values, 6 and 8 percent respectively.

In conclusion can be stated that low-dose CyA therapy was effective in the majority of

patients. Since serum creatinine was relatively insensitive in predicting mild to moderate reductions in renal function, long-term follow-up with precise measurements of GFR and ERPF is mandatory to ascertain the risk of chronic irreversible renal damage.

Introduction

Psoriasis is a multi-factorial skin disease characterized by abnormal keratinocyte proliferation and elevated levels of inflammation causing mediators [1]. A genetically determined disturbance of epidermal immune mechanism probably underlies the disease process [2]. Since the original report of Mueller and Hermann [3], the efficacy of cyclosporin A (CyA) in the treatment of severe psoriasis has been well documented [4-9]. The dose of CyA in these studies, however, varied markedly (1-14 mg/kg/d) and its use had been associated with the occurrence of renal dysfunction and the development of hypertension.

The cellular or molecular mechanisms behind these adverse effects are as yet incompletely understood [10-12]. From the experiences of CyA use in organ transplantation, it appeared that CyA induces a new form of drug toxicity in which functional vasoconstrictory effects consisting of dose-dependent reductions in glomerular filtration rate (GFR) and renal plasma flow (RPF) were accompanied by morphological structural damage in the kidneys [13]. Arteriolopathy (endothelial and smooth muscle cell damage), 'striped' form interstitial fibrosis and focal tubular atrophy have been observed in kidney biopsies obtained from patients treated with high, vasoconstrictory, doses of CyA (8-17.5 mg/kg/d) [13-15].

At present it is unknown whether the dose-dependent, reversible, functional effects of the drug, i.e. renal vasoconstriction, leads to structural renal damage, although there is certainly evidence suggestive of this. It has been shown that the risk of developing irreversible structural alterations in the kidney is closely related to the severity of CyA-induced renal dysfunctions [16].

The genuine concern about CyA-induced nephrotoxicity has resulted in several studies designed to determine the lowest effective dose range [8,17,18] and the use of CyA has been beset by "safety rules" [19-21]. The dose of CyA in autoimmune disorders, particularly in psoriasis, should not exceed 5 mg/kg/d and as soon as unacceptable renal

vasoconstriction occurs i.e. increases in serum creatinine of 30 to 50% over baseline values, the dose of CyA should be reduced. A pooled analysis of data obtained in a large series of psoriatic patients who were treated along these guidelines suggested that strict adherence to these guidelines enabled a reasonably safe use of CyA for a prolonged period [22]. However, proper assessment of the extent of CyA induced renal damage in these patients was hampered by the relative crudeness of serum creatinine as an indicator of glomerular filtration rate (GFR) [23]. Serum creatinine, although widely used clinically to monitor renal function is not an ideal filtration parameter. It is excreted both by glomerular filtration and tubular secretion. Serum creatinine and creatinine clearance thus would be expected to over-estimate GFR at all levels of renal function. Furthermore, CyA even at low-dose is known to exert important functional tubular effects [24] and the possibility that CyA somehow alters the tubular manipulation of creatinine has received insufficient attention. Therefore, the poor correlation between changes in serum creatinine and decline in GFR observed in transplantion and non-transplantion patients treated with CyA is not surprising [25-28]. However, the question whether CyA induced renal dysfunction is completely reversible after CyA is withdrawn, is more important since serum creatinine and creatinine clearance are poor predictors of mild to moderate reduction in GFR. The present Dutch Psoriasis Multicenter Study was undertaken to determine the efficacy and the safety of two low-dose regimens of CyA in 74 patients with severe psoriasis and to assess the reliability of serial serum creatinine measurements to monitor changes in renal function (as reflected by measurements of true GFR in these patients) and to assess the reversibility of renal dysfunction after prolonged CyA treatment (maximum 16 months).

Patients and Methods

Patients

Seventy-four adult patients were enrolled (average age 38 years range 20-75, 45 males and 29 females). They participated in a multi-center study in which two CyA dose schedules (2.5 versus 5.0 mg/kg/d) were compared for induction and maintenance of remission. Six departments of dermatology in the Netherlands co-operated in this trial. The participating centers and the number of patients they included are listed in Table 1. All patients had

severe psoriasis as defined by a Psoriasis Area and Severity Index (PASI) score ≥ 18 [29] [Addendum 1]. The mean PASI score at inclusion was 22 (range 18 - 55) and the duration of the disease ranged from 1 to 46 years (mean 12 years). Exclusion criteria were drug-induced psoriasis eg by lithium or beta-blockers, serum creatinine above 100 μmol/l, bilirubin or liver enzymes above twice the upper limit of the normal range, hyperkalemia, hyperuricemia, hypertension i.e. diastolic blood pressure over 95 mmHg, malignancy or history of malignancy, acute uncontrolled infections, pregnancy, concomitant therapy with nephrotoxic compounds or drugs which are known to interfere with the pharmacokinetics of CyA.

Patients with a history of epilepsy, drug or alcohol abuse or a malabsorption syndrome were also excluded. Previous oral therapy in these patients consisted of methotrexate, retinoids (Neo-Tigason®) or photo-chemotherapy. Results of these therapies are summarized in Table 2. Methotrexate, retinoids or PUVA/UVB were stopped at least 2 weeks and specific local therapy at least 1 week before entry into the study. The protocol was approved by the Ethical Commitee of each participating center and written informed consent was obtained from each patient.

Study design

The study consisted of 3 parts (Figure 1). In Part 1, an open randomized parallel-group study, the efficacy of two dose regimes of CyA (group A, 2.5 mg/kg/d versus group B, 5.0 mg/kg/d) were compared (month 0-3). Patients were randomly allocated to receive one of the dose regimes. Cyclosporin A was taken at mealtimes as soft gelatin capsules of 25 mg and 100 mg in two separate doses and was provided by Sandoz BV, Uden, the Netherlands. Sandoz, Basle, provided the randomization schedule which was stratified for the participating centers. Thirty-two patients were randomized to receive 2.5 mg/kg/d and 42 patients to receive 5.0 mg/kg/d. At the end of month 1 or month 2, a PASI reduction of 10% or more meant continuing the same dose. In case of inefficacy (Failure at month 1 or 2, F_1 or F_2, see Figure 1), i.e. a PASI reduction ≤ 10%, patients from group A could move to group B. For those already in group B, failure meant discontinuation of CyA. At the end of part 1 (month 3) a PASI reduction > 75% or a PASI < 8 was scored as "success". These patients entered part 2 of the study. Patients who did not fulfill these criteria progressed to part 3. A reduction of the PASI score < 10% for those in group A

(failure at month 3, F_3) implied entry into group B.

In Part 2, an open study, we attempted to maintain (month 4-16) the remission induced previously. Patients from group A continued to take 2.5 mg/kg/d CyA until the end of month 12. Patients from group B followed a tapering to 2.5 mg/kg/d CyA at the end of month 7. They then stayed on this dose until the end of month 12. Patients from both groups were tapered off CyA during month 13-16. In case of relapse (month 7-12), defined as an increase of the PASI > 50% above baseline, the dose of CyA was temporarily increased to 5.0 mg/kg/d and then tapered down to zero again during month 13-16. After a second relapse patients entered part 3. At any time during parts 1 and 2 of the study, the CyA dose was reduced by 25% in case of adverse events such as a rise in serum creatinine > 30% over baseline or above 130 μmol/l, a rise in serum potassium above 5.5 mmol/l or definite liver dysfunctions. If the abnormality had not improved by the next visit, a further 25% dose reduction was carried out. If this failed to achieve the desired effect, CyA had to be withdrawn and the patient entered into Part 3.

All patients who had received CyA for some time (3-16 months) had to participate in Part 3 of the study, a post-treatment period lasting 3 months, in which the reversibility of any CyA-induced abnormality was assessed.

Efficacy

A global rating that reflected the percentage and severity of body quadrants affected by psoriasis, ranging from 0 to 72, the psoriasis area and severity index (PASI) [29] was evaluated at each visit. Each patient was seen by the same physician at all visits, with a few exceptions.

Measurements of renal function

Serum creatinine and creatinine clearance

Evaluation of CyA-associated renal dysfunction was based on serum creatinine levels and a modified Cockcroft formula [30] predicting creatinine clearance (C_{cr}) from serum creatinine, body weight, age and sex.

$$\text{Males} : C_{cr} = \frac{28 - 0.2 * \text{age (yr)}}{\text{serum creatinine } (\mu\text{mol/l})} * \text{bodyweight(kg)} * 6.15$$

Females: $C_{cr} = \frac{24 - 0.2 * \text{age (yr)}}{\text{serum creatinine } (\mu\text{mol/l})} * \text{bodyweight(kg)} * 6.15$

Results are expressed as absolute values and as percentage increase over baseline. In the first 3 months induction period, serum creatinine was measured every week for the first month and then at the end of weeks 6, 8 and 12. In addition to values taken at a fixed time-point, the maximum serum creatinine concentration (or increase) and matching predicted creatinine clearance with CyA treatment were selected as a key parameter. This was because renal dysfunction was often transient as the dose was reduced each time it occurred. The maximum value during the treatment period for each patient was thus a true reflection of renal dysfunction. During the maintenance and 3 months post-treatment period, serum creatinine was measured every 4-6 weeks. To establish reversibility of CyA-associated changes in serum creatinine, the highest levels during the induction phase were compared with the last values obtained during the post-treatment period.

Glomerular filtration rate (GFR) and effective renal plasma flow (ERPF)

GFR and ERPF were measured at baseline, months 3 and 12 and finally 1-3 months after cessation of CyA. At the 4 centers which participated in these measurements, two different techniques were used. Two centers used single-shot techniques without urine collection [31]. Our center (University Hospital Rotterdam Dijkzigt) and the center at the Free University Hospital Amsterdam used the more laborious constant-infusion method with urine collection [32,33]. With the last method glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were measured simultaneously as the clearance of ^{125}I-iothalamate and ^{131}I-orthoiodohippurate (Amersham, UK) respectively. After priming doses of 0.1 μCi/kg body weight of thalamate and 0.3 μCi/kg body weight of hippuran, the radiolabels were infused at constant rates of 0.2 and 0.05 μCi/min, respectively. After an equilibrum period of 120 minutes, two clearance periods were obtained. These periods varied in length (20 to 40 min) depending on the subject's ability to void. Urine was collected without the use of a bladder catheter in order to avoid the risk of infection. Water and soft drinks were given freely in order to induce urine production in the order of 300 to 500 ml/hour. Blood samples were taken at the start and end of each clearance period from a cannula placed in the brachial vein of the non-infused arm. Radioactive counts of ^{125}I-iothalamate and ^{131}I-iodohippurate in the plasma and urine were measured

using a gamma scintillation counter. The standard formula, $C_x = (U_x V)/P_x$ was used to calculate clearance values. U_x and P_x denote urine and plasma concentration of the radiolabels, C_x stands for clearance and V is urine flow rate. The mean GFR and ERPF ware calculated from the two clearance periods. Coefficients of variations for GFR and ERPF were 8 and 11% respectively.

At the other centers GFR was measured by the rate at which ^{51}Cr-edetic acid (^{51}Cr-EDTA) disappeared from the plasma. At 2, 3 and 4 hours after injection, blood samples were taken and GFR was calculated according to the mathematical model of Bröchner-Mortensen [31]. ERPF was estimated from a single injection of ^{131}I-orthoiodohippurate. A blood sample was drawn at 44 min after injection. The ratio of injected-dose counts to plasma counts was used to calculate ERPF using the empirical equation derived by Tauxe et al [34]. Standard errors of GFR and ERPF determined by the single shot technique were reported by these centers to be 6 ml/min and 10 ml/min respectively.

Blood pressure

Blood pressure was measured with a mercury sphygmomanometer after a few minutes rest at each clinical visit. Elevated blood pressure was defined according to the World Health Organization (WHO) definition (systolic BP $\geq$ 160 mmHg or diastolic BP $\geq$ 95 mmHg). If a patient had persistent elevated blood pressure (at three consecutive visits) antihypertensive therapy was started as recommended in the protocol. More detailed measurements of blood pressure and heart rate (every 15 minutes for 3 hours) were performed at the centers in Rotterdam and Amsterdam during the renal function studies with automatic semicontinuous oscillometric blood pressure measurement devices (Accutorr, Dinamap).

Routine serum chemistry and cyclosporin assay

Blood CyA levels were measured using radioimmunoassay. A monoclonal antibody was used to characterize the parent drug [35]. Unless stated otherwise, all blood samples were collected in EDTA tubes before administration of CyA ("trough"). Haemoglobine, total white blood cell count, platelets, uric acid, potassium, magnesium, total bilirubin, liver enzymes and glucose were also determined, and at regular intervals urine was checked for protein and glucose.

Statistical analysis

Results are presented as mean $\pm$ 1 s.e.m. on median and range. Differences within assigned treatment groups were evaluated by paired t-test and differences between groups by unpaired t-test. When exploratory data analysis showed significant deviations from the normal distribution or inequality of variances, non-parametric tests were used (Wilcoxon matched pairs rank sum test and Mann-Whitney rank sum test). Correlations among variables were determined by calculation of Spearman's rank correlation coefficient. All p-values are two-tailed. Data were analyzed with the Statistical Package for the Social Sciences (SPSS inc., Chicago, Illinois, U.S.A.)

Results

Part 1 - Induction period, months 0-3

Efficacy of cyclosporin treatment

From the 74 patients enrolled and randomized, 64 patients completed the 12 weeks treatment with CyA (Table 3). At the 2.5 mg/kg/d dose regime (group A, n=32), there was a PASI reduction of 30% after 4 weeks of treatment. This was rather low. It contrasted sharply with the 73% response in the 42 patients randomized in group B. The administration of the two initial doses of CyA resulted in substantial overlap among the patients' average blood trough levels between the second and the fourth week. The correlations between relevant variables and dose and blood levels of CyA after four weeks of fixed dose therapy are shown in Table 4. At that time clinical improvement as reflected by the PASI score did not correlate with the dose any better than with the trough blood level of CyA.

Twelve of the non-responders in group A continued with CyA at 5.0 mg/kg/d. Ten of them responded to the treatment. The PASI scores of the 20 patients who were finally treated with 2.5 mg/kg/d and the PASI scores of the 44 patients who were treated with 5.0 mg/kg/d or less are shown in Figure 2. Response rate and effectiveness differed significantly in both groups. The correlation between the reduction of the PASI score and the duration of the active disease, the initial level of the PASI score and age of the patients was low. The following trend was observed: longstanding psoriasis was characterized by a higher initial PASI score that responded better to CyA in part 1 of the trial. During the

whole induction period trough levels of CyA showed an enormous interindividual variation (Figure 3). Nevertheless, there was a significant correlation between the dose and the average blood level of parent CyA (r=.42, p=.0000, n=495 measure points).

Side-effects and safety of cyclosporin treatment

The side-effects observed during CyA treatment are listed in Table 5. Only in two patients from group A, CyA had to be stopped, in one because of a rise in serum creatinine of more than 30% above baseline (78 to 113 μmol/l) and in the other because of hypertension. Dose reduction, however, because of renal dysfunction and/or hypertension was necessary in 10 out of the 42 patients randomized in group B. Figure 4 shows a time plot of the effects of CyA on blood pressure and renal function in the 64 patients who completed the 12 weeks treatment period (20 patients had received 2.5 mg/kg/d, 44 patients had received 5.0 mg/kg/d or the reduced dose). CyA induced a dose-dependent increase of serum creatinine and a decrease of calculated creatinine clearance. Changes in the clinical and the laboratory variables during the induction period (fixed-dose phase versus the adjusted-dose phase) are summarized in Table 6. Serum creatinine in the patients receiving 2.5 mg/kg/d did not change significantly. The maximum increase of creatinine, however, at some time during the 12 weeks period was 15±2% (baseline serum creatinine level 82±3 μmol/l, peak values 94±3 μmol/l). For the 44 patients treated with 5.0 mg/kg/d or less, serum creatinine rose from 80±2 to 87±3 μmol/l with peak levels of 98±3 μmol/l (+23±3%).

From the 64 patients who completed the induction period, detailed measurements of the GFR were obtained in 44 patients (Figure 5). ERPF was determined in 27 patients. After twelve weeks of treatment, the GFR and ERPF decreased by a mean of 13 and 19% respectively, in the patients receiving 2.5 mg/kg/d CyA (group A, n=16) and 15 and 14% in those receiving a mean dose of 4.8 mg (group B plus non-responders group A, n= 28) (Table 6). In the latter group the decrease in the GFR was accompanied by a significant rise in serum creatinine and calculated creatinine clearance. In contrast, the decrease in GFR in the patients of group A was not apparent from measurements of serum creatinine. As already mentioned, twelve patients initially randomized in group A were switched to group B because of clinical inefficacy. This should be taken into account when group differences are considered. For all patients of group A and B together (Figure 6), GFR

decreased from 121±64 ml/min at baseline to 99±4 ml/min at the end of the induction period (decrease of 14±2%, $p<0.017$). The decrease of ERPF was in the same order of magnitude, 12±3% (baseline, 504±35 ml/min; week 12 CyA, 428±22 ml/min, $p<0.01$). Filtration fraction did not change significantly. Regression analysis demonstrated that change in serum creatinine was a poor predictor of changes in the GFR. A weak correlation was observed between the change in serum creatinine and the change in GFR ($r=0.32$, $p<0.05$, $n=44$). The change in calculated creatinine clearance correlated slightly better with the change in GFR ($r=0.38$, $p<0.05$).

Part 2 - Maintenance and tapering period (4-16 months)

The number of dropouts during this period was considerable. From the 64 patients that entered this part of the study, only 14 completed part 2 of the trial completely till month 16. The actual numbers and the reasons for dropping out are shown in Tables 7 and 8. For most patients (23 out of 49) relapse of the disease and therefore unwillingness to go through with the rather long tapering phase was the main reason to leave the study prematurely. This is reflected by the actual moment of dropping out i.e. the step-wise decrease in the dose at the end of months 6, 12 and 15. Dropouts, dose reductions and re-entries resulted in a rather heterogenous group in which the results of clinical and laboratory parameters could not be related to the original 2.5 or 5.0 mg/kg/d doses. From the 44 patients who took part in the nephrological study during the induction period (months 0-3), detailed measurements of blood pressure and renal function after CyA treatment for at least 12 months was obtained in 21 patients. The main findings are summarized in Table 9. Prolonged CyA treatment did not lead to an additional reduction in GFR and ERPF. On the contrary, the gradual reduction of the dose to 2.5 mg/kg/d dictated by the protocol led to an improvement in renal functions and a decrease in blood pressure. Baseline values, however, were not reached.

Part 3 - Post-treatment observation

From the 64 patients who were treated with CyA for at least 3 months, reversal of CyA-induced renal dysfunction was observed in 53 patients (at least one measurement of serum creatinine after stopping CyA). The percentage changes are shown in Figure 6. At 1-3 months after stopping CyA, the creatinine level was 0±2% higher (not significant) than

baseline. For the 32 patients whose GFRs were measured after stopping CyA therapy, mean GFR was 113±5 ml/min during the post-treatment period compared with 121±6 ml/min before CyA treatment (decrease 6±2 %, $p<0.01$). ERPF (measured in 26 patients) also did not return to pre-treatment values. It remained 8±2 % ($p<0.01$) below baseline. In contrast, serum creatinine and predicted creatinine clearance also in this subset of patients did not differ significantly from baseline values.

Discussion

The present Dutch Multi-Center Study confirms earlier reports (4,6,8,18) that low-dose cyclosporin A is an effective therapy for severe psoriasis. Our results suggest that an appropriate initial dose of CyA lies between 2.5 and 5.0 mg/kg/d. When resolution of the lesions is relatively unimportant, 2.5 mg/kg/d may be a good starting dose as it has less side-effects. In addition, 83% of the treatment failures using 2.5 mg were successful after the dose was increased to 5.0 mg/kg/d. Hence, tachyphylaxis did not occur in patients who started with a low dose. Conversely, approximately 20% of the patients who were treated with 5.0 mg/kg/d required dose adjustments because of adverse effects.

Improvement in psoriasis was maintained in the majority of patients taking a consistent dose of CyA. In the 5.0 mg/kg/d group, attempts to reduce the dose to 2.5 mg/kg/d resulted in a high relapse rate. Thus it seems very likely that the maintenance dose is very close to the minimum effective dose. Relapses did occur in nearly all our patients after stopping CyA. Continuous therapy, therefore is necessary for a long period of time.

Psoriasis, however, is not a life-threatening disease and the long-term use of a potentially harmful drug such as CyA must be carefully evaluated and monitored. The main concern in the use of CyA is the risk of irreversible renal damage.

Therefore, in the present study, recommendations described in the introduction were strictly adherent in order to minimize the adverse effects of CyA. Dose adjustments because of a rise in serum creatinine of greater than 30% over baseline were carried out in 11 (14%) out of 74 patients. Adjusting the CyA dose on the basis of serum creatinine resulted in a stable creatinine level in our patients. The effect of CyA on the GFR was measured in 35 out of 44 patients and these results are compared with other reports in Table 10. With regard to long-term nephrotoxicity, the GFR and ERPF did not decrease

further in our 21 patients who were treated with CyA for one year. On the contrary, at an average dose of 3.7 mg/kg/d the GFR was 8% below baseline (14% at 3 months) and the ERPF was 9% lower (15% at 3 months). None of our patients developed protracted renal dysfunction and no significant difference in mean creatinine concentration as compared to baseline was observed 3 months after stopping treatment.

Does this mean that no harm was done to the kidney? We are not so sure! Glomerular filtration rate (n=33) and effective renal plasma flow (n=26) after cessation of CyA in patients who were treated for an average of 9 months (range 3-16) were significantly different from baseline values. GFR and ERPF in fact remained $6\pm2\%$ and $8\pm2\%$ respectively, below the values measured prior to therapy. In contrast, serum creatinine and calculated creatinine clearance had returned in this subgroup as well, to the pretreatment values. Therefore, the validity for assessing the reversibility of CyA-associated renal dysfunction based on serum creatinine measurements alone should be questioned.

In our patients, the relation between the rise in serum creatinine and the fall in GFR was weak indicating that during treatment with CyA, serum creatinine levels can be used only as a very rough guide for GFR. Our results confirm findings in renal and non-renal transplant patients who were treated with CyA. In these patients there was also a poor correlation between changes in serum creatinine and decline in GFR [25,37].

Besides the effects of CyA on GFR, we were rather concerned by a lack of return of ERPF to baseline values after cessation of CyA. It could imply that renal vasospasm early in the course of CyA therapy in time results in some structural alteration of the renal vascular bed. In this regard, determination of renal blood flow is more discriminating than GFR, because the single nephron GFR of remnant glomeruli that remain perfused could be adaptively increased, thereby, compensating for the declining number of functional nephrons. Histopathological observations in heart transplant recipients [38] suggested that the cortical microvasculature had undergone progressive damage and alterations due to continuous treatment with CyA beyond 12 months.

However, all reports on the occurrence of CyA nephropathy in transplant recipients and in autoimmune diseases were based on initial CyA doses of higher than 7 mg/kg/d. In contrast, in patients with lupus erythematosus or rheumatoid arthritis on 5 mg/kg/d [21] and psoriasis patients on 3,9 mg/kg/d [16] treated for 14-42 and 3-37 months respectively only slight morfological changes were observed in the kidneys.

In view of our findings, it is relevant to question whether the increasing use of CyA for treating psoriasis is justified. Since the disease tends to recur after CyA is withdrawn, prolonged or even permanent administration of the drug is likely to be required. Although our study among others clearly shows that therapeutic efficacy can be achieved at CyA doses lower than those used in the past, we cannot exclude that, at least in some patients, harm could have been done to the kidney. Nevertheless, our preliminary experience in monitoring GFR and ERPF is encouraging. Although a significant number of patients had decreased renal function at some point during the study, most episodes improved or resolved with dose adjustment or discontinuation of the drug. In the few patients with persistently decreased GFR and ERPF after cessation of CyA, the drug-free period varying between 1-3 months was perhaps too short for a full recovery. Whatever the reason, serum creatinine and creatinine clearance appeared to be poor predictors of mild to moderate reduction in GFR in long-term treatment regimes with CyA. Our findings underscore the plea by Myers [38] and others [21,28,39] to monitor GFR during these regimes by other means than creatinine determinations alone (e.g. inulin or radiolabelled thalamate, EDTA or DTPA). If pretherapy and interval GFR determinations are performed and CyA dose adjustments do not alleviate the depression of GFR, other forms of treatment should be considered. Clearly, additional studies are required to establish the risk of chronic irreversible renal damage. For the time being, in patients requiring long-term systemic therapy, it is problably wise to alternate systemic treatment regimes (cyclosporin A, methotrexate, photo-chemotherapy, retinoids) to reduce the toxicity of each type.

Table 1. Participating centers and numbers of patients they included

center	number of patients
1. Rotterdam, University Hospital Dijkzigt	12
2. Amsterdam, Free University Hospital	12
3. Maastricht, University Hospital St. Annadal	16
4. Heerlen, De Wever Hospital	14
5. Helmond, St. Lambertus Hospital	10
6. The Hague, Leyenburg Hospital	10
	74

Table 2. Treatment with methotrexate, retinoids and PUVA, before start of cyclosporin A. Number of patients and period of treatment. Response: 1=weak, 2=fair, 3=good. Remission period in weeks

treatment	number of patients (%)	periods of treatment (range, median)	response 1 2 3	remission in weeks (median)
methotrexate	16 (22%)	16 (1-11, 15)	3 8 5	0-76 (2)
retinoids	29 (39%)	29 (1- 9, 1)	4 13 12	0-80 (2)
PUVA	56 (76%)	56 (1- 8, 2)	11 20 25	0-99 (4)

Table 3. Summary of number of patients that could be scored as success, dose adaptations and drop-outs (for reasons see text) in part 1, of group A and B

Group A	original in A	switch A to B	total	Group B
success	17	10	27	36
drop-out	3	2	5	6
total	20	12	32	42
dose reduction	1	2	3	10

Table 4. Changes in clinical and laboratory variables in relation to dose of cyclosporin A and mean blood levels of cyclosporin A during fixed-dose phase (first four weeks)

	Dose		Blood Level	
	r (n)	P value	r (n)	P value
Psoriasis area and severity index	−0.28 (84)	<0.01	−0.29 (60)	<0.05
Systolic blood pressure	0.08 (84)	NS	0.17 (60)	NS
Diastolic blood pressure	0.22 (84)	<0.05	0.40 (60)	<0.001
Mean blood levels	0.39 (60)	<0.01		not applicable
Serum creatinine	0.01 (84)	NS	0.25 (60)	0.06
Calculated creatinine clearance	−0.05 (51)	NS	−0.39 (51)	<0.01
Serum uric acid	−0.08 (77)	NS	0.21 (57)	NS
Serum potassium	0.22 (81)	<0.05	0.13 (59)	NS
Serum magnesium	−0.30 (70)	<0.01	−0.34 (49)	<0.02
Serum total bilirubine	0.26 (60)	<0.05	0.47 (60)	<0.001
Body weight	0.18 (82)	NS	0.21 (60)	NS

r denotes Spearman's rank-correlation coefficient. n refers to the number of patients included in the computation of r. NS denotes not significant. P values are two-tailed. The absolute change in the variable from before therapy to the fourth week was used for this analysis.

Table 5. Summary of side-effects: according to actual dose of cyclosporin A, at any time of the induction period (%)

	2.5 mg/kg/d	5 mg/kg/d
subjective complaints		
headache, dizziness	7 (22)	9 (21)
fatigue	1 (3)	1 (2)
paraesthesias, tremor	2 (6)	13 (31)
muscle or joint pain	2 (6)	3 (7)
gastrointestinal symptoms	3 (9)	8 (19)
premature heart beats	–	1 (2)
chills	–	2 (5)
upper airway irritation	3 (9)	2 (5)
burning eyes, ear pain	1 (3)	4 (10)
objective signs		
hypertension	1 (3)	7 (17)
gum hyperplasia	1 (3)	3 (7)
hypertrichosis	2 (6)	10 (24)
acne vulgaris	–	1 (2)
potassium (>5.5 mmol/l)	–	4 (10)
creatinine (>30% over baseline)	–	9 (21)
bilirubin (twice upper limit)	–	2 (5)
basocellular carcinoma	–	1 (2)

Table 6. Changes in clinical and laboratory variables during the induction period

	After 4 weeks (fixed-dose)		After 12 weeks (adjusted dose)	
	2.5 mg	5 mg	3.5 mg	4.8 mg
	mean ± SE percent change		mean ± SE percent change	
	n=30	n=42	n=20	n=44
PASI	−40 ± 5	−62 ± 3*	−80 ± 3	−85 ± 3
Blood pressure				
systolic	−3 ± 2	0 ± 1	−2 ± 2	3 ± 2
diastolic	−3 ± 2	5 ± 2***	0 ± 2	5 ± 2
Creatinine	7 ± 3	11 ± 3	3 ± 2	11 ± 2**
Creatinine clearance	−5 ± 3	−7 ± 2	−2 ± 2	−7 ± 2*
Glomerular filtration rate	–	–	−13 ± 2	−15 ± 2
Effective renal plasma flow	–	–	−19 ± 2	−14 ± 2
Uric acid	10 ± 6	8 ± 3	3 ± 2	4 ± 2
Magnesium	−2 ± 5	−14 ± 2**	−6 ± 2	−10 ± 1
Potassium	1 ± 1	4 ± 1	0 ± 2	4 ± 1
Bilirubine (total)	27 ± 12	63 ± 12	34 ± 13	56 ± 11
Body weight	−1 ± 1	1 ± 1	0 ± 1	1 ± 1

* <0.05

** <0.01 difference between groups

*** <0.001

Table 7. Actual moment of drop-out in phase 2, related to cause, for group A and group B together

month / cause	3	4/5	6/7	8/9	10/11	12/13	14/15
renal dysfunction	1	2	–	1	1	1	–
hypertension	–	–	–	1	1	1	–
relapse	–	2	4	2	2	4	9
uncooperative	2	1	2	2	1	–	1
side-effects	1	3	–	–	–	1	1

Table 8. The causes and number of drop-outs in phase 2, for all centers*, and number of patients that completed the study till month 16-19

center / cause	1	2	3	4	5	6	(all)
renal dysfunction	1	1	1	–	2	–	(5)
hypertension	–	–	1	1	1	–	(3)
relapse	1	9	5	4	–	4	(23)
uncooperative	2	1	2	4	–	3	(12)
side-effects**	1	–	3	1	1	–	(6)
drop-outs	5	11	12	10	4	7	(49)
completed	3	–	–	3	6	2	(14)

* see Table 1.
** hypertrichosis (4), depression (1), thyroid disease (1)

Table 9. Effects of one year exposure to cyclosporin A on blood pressure and renal function

Patients n=21	Baseline mean ± SEM	Time of exposure to CyA 3 months mean ± SEM	12 months mean ± SEM
Blood pressure* (mmHg)	116 ± 3/72 ± 2	130 ± 4/81 ± 4 a/a	122 ± 3/74 ± 3 a,b/b
Heart rate (bpm)	67 ± 2	68 ± 2	65 ± 2
Serum creatinine (μmol/l)	78 ± 3	85 ± 4 a	86 ± 4 a
Glomerular filtration rate (ml/min)	111 ± 7	96 ± 4 a	102 ± 6 a
Effective renal plasma flow (ml/min) (n=16)	492 ± 50	421 ± 27 a	451 ± 33 a

a denotes values that do differ significantly from baseline

b denotes values that do differ significantly from values at 3 months

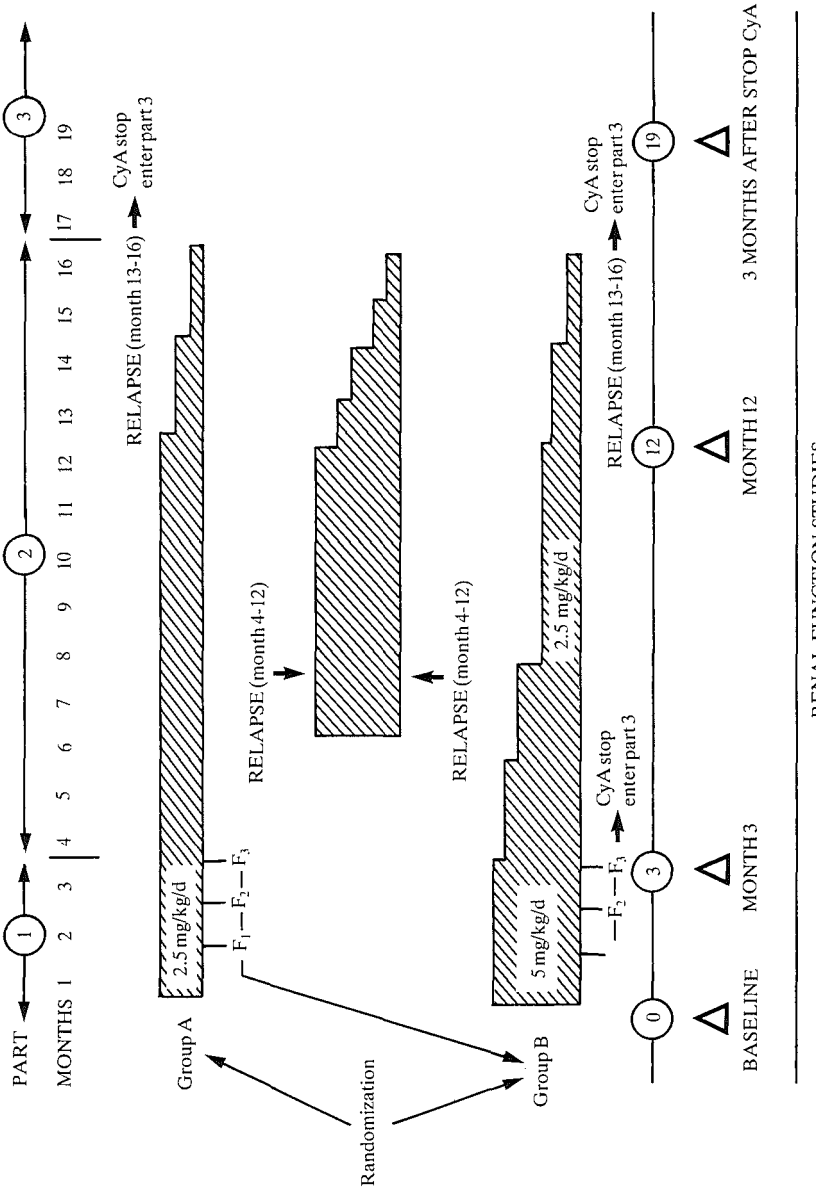
* measurements by an automatic blood pressure measurement device

Table 10. Effect of cyclosporin A on the glomerular filtration rate (GFR)

Study [ref]	period (wks)	CyA dose (mg/kg/d)	decline of GFR	no. of patients
this study	12	4,3	− 15%	35
Powles et al [36]	9	3	− 10%	11
Ellis et al [18]	8	5,2	− 16%	34
Gilbert et al [28]	9	4,7	− 52%*	5

* concomittant use of diuretics and NSAIDs was allowed in this study.

Figure 1. Study design



$F_{1,2}$ = failure at end of month 1 and 2 = PASI ≥ 90% of baseline value
F_3 = failure at end of month 3 = PASI > 8 (unless ≤ 25% of baseline value)
Relapse = PASI > 50% of baseline

Fig. 2.

Mean Psoriasis Area and Severity Index (PASI) per week for group A and group B in part 1.

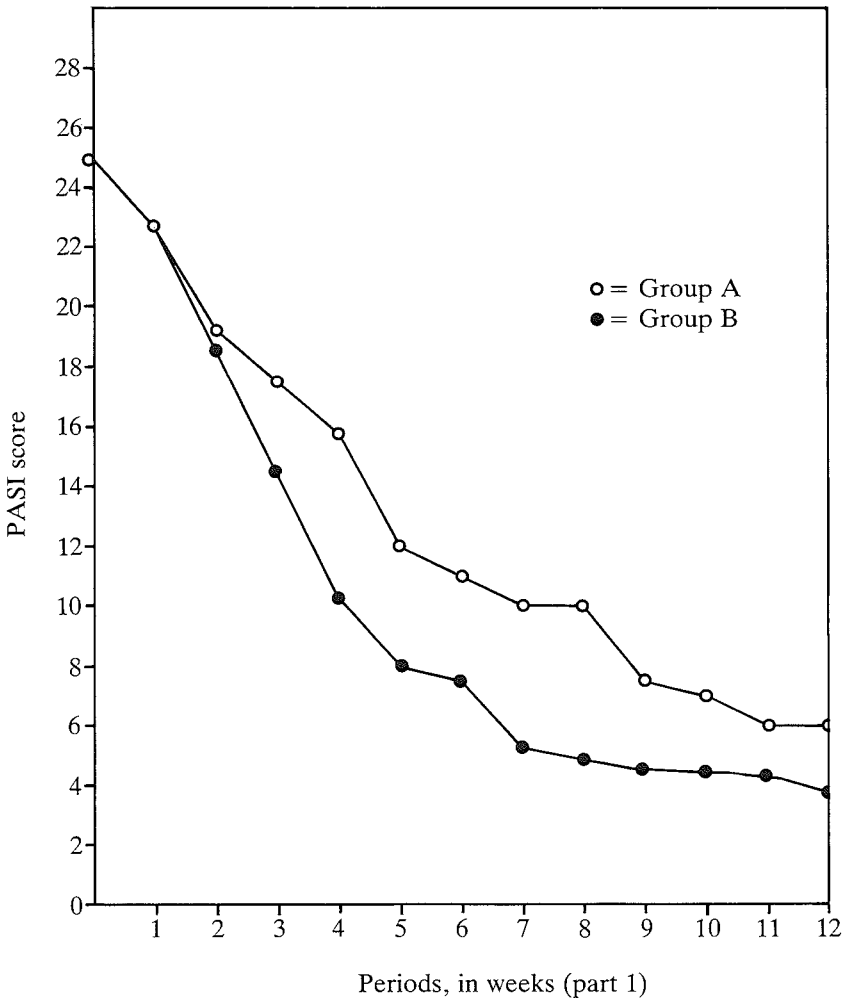


Fig. 3.

Plot-diagram of parent cyclosporin A whole blood trough levels (ng/ml) versus dosage of the oral formulation (mg/kg/d) of 495 measure points, and regression (slope .41568, sig .0000) See text. o= 1, ●= 10

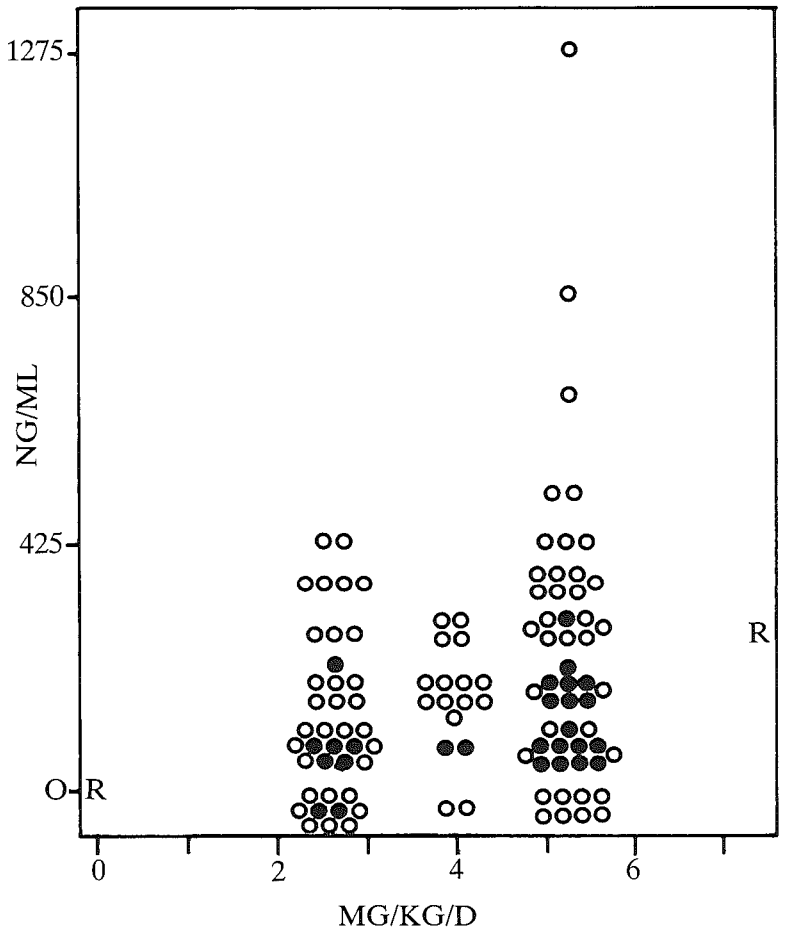


Fig. 4.

Cockroft clearance (ml/min), serum creatinine (μmol/l) and cyclosporin A dose (mg/kg/d), in week 0-12, for group A (2.5 mg/kg/d) and group B (5 mg/kg)d)

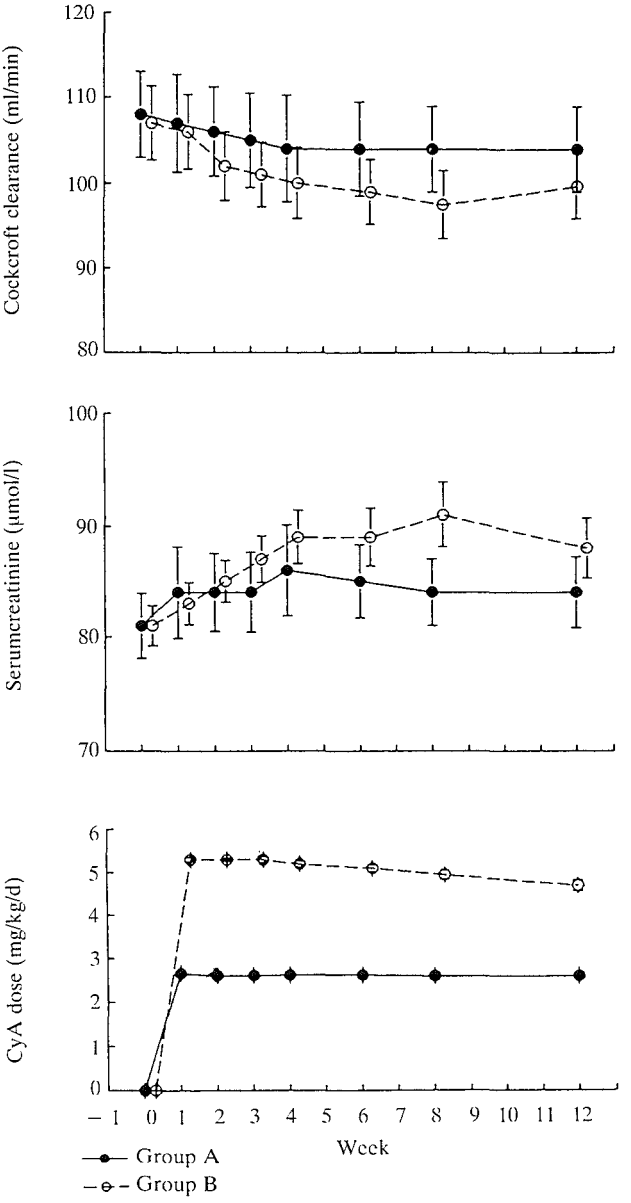


Fig. 5.

Changes in glomerular filtration rate (ml/min) and effective renal plasma flow (ml/min), values of baseline and CyA therapy compared (see text)

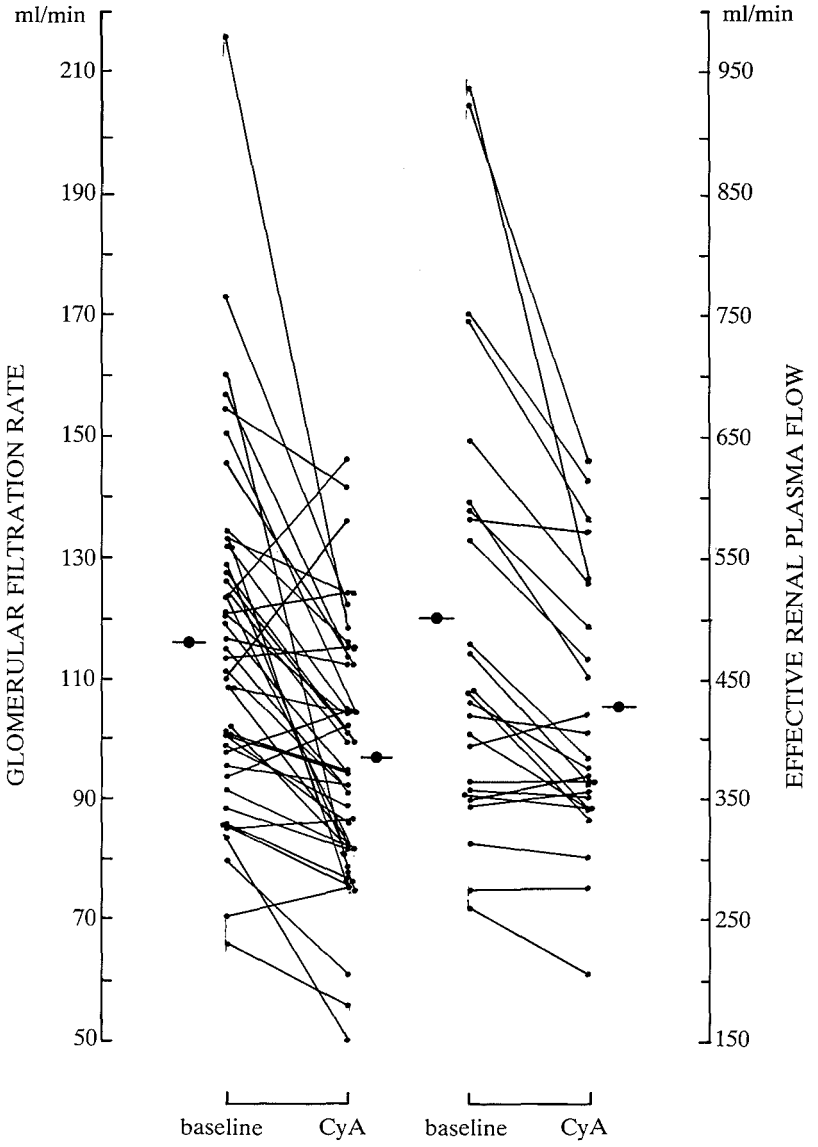
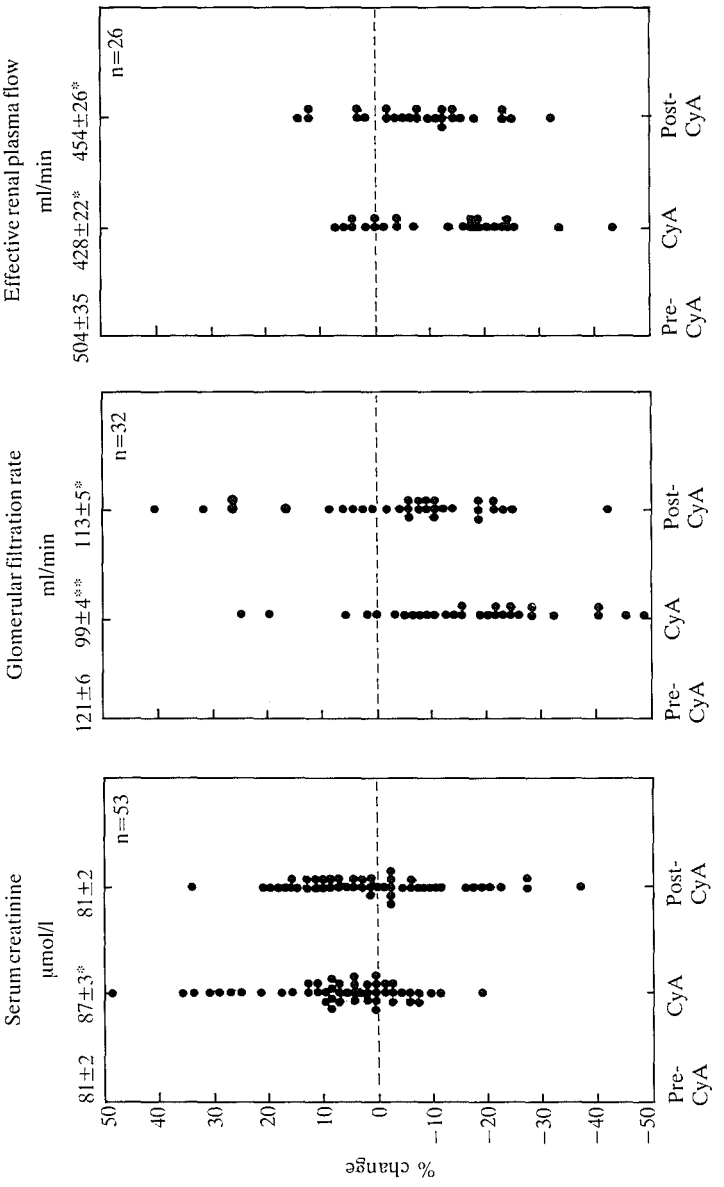


Fig. 6.

Time plot diagrams of changes (%) in values of serum creatinine (μmol/l), glomerular filtration rate (ml/min), effective renal plasma flow (ml/min) with mean values (*p <0.01, **p <0.017), before during (month 3) and after CyA therapy (part 3), for group A and B together



References

1 Mier PD, van de Kerkhof PCM, ed. Textbook of psoriasis. Edinburgh: Churchill Livingstone, 1986.

2 Bos JD. The pathomechanisms of psoriasis; the skin immune system and cyclosporin. Br J Dermatol 1988; 118: 141-56.

3 Mueller W, Hermann B. Cyclosporin A for psoriasis. N Engl J Med 1979; 301: 555.

4 Van Joost Th, Heule F, Stolz E et al. Short-term use of cyclosporin A in severe psoriasis. Br J Dermatol 1986; 114: 615-20.

5 Ellis CN, Gorsulowsky DC, Hamilton TA et al. Cyclosporine improves psoriasis in a double-blind study. JAMA 1986; 256: 3110-6.

6 Griffiths LEM, Powles AV, Leonard JN et al. Clearance of psoriasis with low-dose cyclosporin. Br Med J 1986; 293: 731-2.

7 Picascia DD, Garden JM, Frenkel RK et al. Treatment of severe psoriasis with systemic cyclosporin. J Am Acad Dermatol 1987; 408-14.

8 Timonen P, Friend D, Abeywickrama K et al. Efficacy of low-dose Cyclosporin A in psoriasis; results of dose-finding studies. Br J Dermatol 1990; 122 (suppl 36): 33-9.

9 Heule F, Bousema MT, Laeijendecker R et al. Three long-term regimens with cyclosporin for psoriasis. Acta Dermatol Venereol (Stockh) 1989; 146: 171-5.

10 Mason J. The pathophysiology and toxicology of Sandimmun[r] in man and in animals. Pharmacollogy of cyclosporine (Sandimmune). VI. 1989; 42: 423-34.

11 Schachter M. Editorial Review. Cyclosporin A and hypertension. J of Hypertension 1988; 6: 511-6.

12 Dieperink H. Cyclosporin A nephrotoxicity. Dan Med Bul 1989; 36: 235-48.

13 Mihatsch MJ, Thiel G, Spichtin HP et al. Morphological findings in kidney transplants after treatment with cyclosporin. Transplant Proc 1983; 15: 2821-35.

14 Klintmalm G, Bohman SO, Sundelin B et al. Interstitial fibrosis in renal allografts after 12 to 40 months of cyclosporin treatment. Beneficial effects of lower doses early after transplantation. Lancet 1984; ii; 950-4.

15 Myers BD, Ross J, Newton L et al. Cyclosporine-associated chronic nephropathy.

N Engl J Med 1984; 311: 699-705.

16 Mihatsch MJ, Thiel G, Ryffel B. Renal side-effects of cyclosporin A with special reference to autoimmune diseases. Br J Dermatol 1990; 122 (suppl 36): 101-15.

17 Van Joost Th, Bos JD, Heule F et al. Low-dose cyclosporin A in severe psoriasis. A double-blind study. Br J Dermatol 1988; 118: 183-90.

18 Ellis CN, Fradin MS, Messana JM et al. Cyclosporine for plaque-type psoriasis - results of a multidose, double-blind trial. N Engl J Med 1991; 324: 277-84.

19 Mihatsch MJ, Thiel G, Ryffel B. Hazards of cyclosporin A therapy and recommendation for its use. J Autoimmun 1988; 1:533-43.

20 Bos JD, Meinardi MMHM, van Joost Th. Use of cyclosporin in psoriasis. Lancet 1989; ii: 1500-2.

21 Anonymous. A concensus report cyclosporin A therapy for psoriasis [Editorial]. Br J Dermatol 1990; 122 (suppl 36): 1-3.

22 Feutren G, Abeywickrama K, Friend D et al. Renal function and blood pressure in psoriatic patients treated with cyclosporin A. Br J Dermatol 1990; 122 (suppl 36): 57-69.

23 Levey AS. Nephrology forum; measurement of renal function in chronic renal disease. Kidney Int 1990; 38: 167-84.

24 Dieperink H, Starklint H, Leyssac PP. Nephrotoxicity of cyclosporin A in an animal model. A study of the nephrotoxic effect of cyclosporin on overall renal and tubular function in conscious rats. Transplant Proc 1983; 15/4 (suppl): 2736-42.

25 Tomlanovich S, Golbetz H, Perlroth M et al. Limitations of creatinine in quantifying the severity of cyclosporine-induced chronic nephropathy. Am J Kidney Dis 1986; 8: 332-7.

26 Ross RA, Wilkinson A, Hawkins RA et al. The plasma creatinine concentration is not an accurate reflection of the glomerular filtration rate in stable renal transplant patients receiving cyclosporine. Am J Kidney Dis 1987; 10: 113-7.

27 Palestine AG, Austin HA, Balow JE et al. Renal histopathologic alterations in patients treated with cyclosporine for uveitis. N Engl J Med 1986; 314: 1293-8.

28 Gilbert SC, Emmett M, Menter A et al. Cyclosporine therapy for psoriasis; serum creatinine measurements are an unreliable predictor of decreased renal function. J Am Acad Dermatol 1989; 21: 470-4.

29 Frederiksson T, Petterson U. Severe psoriasis-oral therapy with a new retinoid. Dermatologica 1978; 157: 238-44.

30 Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16: 31-41.

31 Brochner - Mortensen J. Routine methods and their reliability for assessment of glomerular filtration rate in adults. Dan Med Bull 1978; 25: 181-202.

32 Schalekamp MADH, Schalekamp-Kuyken MPA, Birkenhäger WH. Abnormal renal haemodynamics and renin suppression in hypertensive patients. Cli Sc 1970; 38: 101-10.

33 Donker AJM, van der Hem GK, Sluiter WJ et al. A radio-isotope method for simultaneous determination of the glomerular filtration rate and the effective renal plasma flow. Neth J Med 1977; 20: 97-103.

34 Tauxe WN, Dubovsky EV, Kidd TE. Comparison of measurement of effective renal plasma flow by single plasma sample and plasma disappearance slope/volume methods. Eur J Nucl Med 1984; 9: 443-5.

35 Ball PE, Munzer H, Keller HP et al. Specific ^{3}H-radioimmunoassay with a monoclonal antibody for monitoring cyclosporine in blood. Clin Chem 1988; 34: 257-60.

36 Powles AV, Carmichael D, Hulme B et al. Renal function after long-term low-dose cyclosporin for psoriasis. Br J Dermatol 1990; 122: 665-9.

37 Poplawski S, Gonwa T, Goldstein R et al. Long-term nephrotoxicity in liver transplantation. Transplant Proc 1989; 21: 2469-71.

38 Myers BD, Sibley R, Newton L et al. The long-term course of cyclosporine-associated chronic nephropathy. Kidney Int 1988; 33: 590-600.

39 Messane JM, Rocher LL, Ellis CN et al. Effects of cyclosporine on renal function in psoriasis patients. J Am Acad Dermatol 1990; 23: 1288-93.

Chapter 8

Treatment regimes and safety guidelines for use of cyclosporin A in severe psoriasis

This chapter is mainly based on the following manuscripts:

Treatment regimens in severe psoriasis vulgaris with cyclosporin.
Van Joost Th, Tank B, Heule F, Wenting GJ.
Journal of Dermatological Treatment 1991; 1: 311-

Use of CyA in psoriasis.
Bos JD, Meinardi MMHM, Van Joost Th, Heule F, Powles AV, Fry L.
Lancet 1989; ii: 1500-2.

Summary

In recent years, much attention has been focussed on cyclosporin A (CyA) as a new alternative drug for the treatment of recalcitrant disabling psoriasis vulgaris. This drug has the important advantage of being non-myelotoxic as compared to other immunosuppressants. In conjunction with the earlier reported data concerning the clinical use of CyA to treat severe psoriasis, three treatment schedules are outlined: short-term, intermittent and long-term. Uncontrolled treatment of psoriasis with CyA could increase the risk of irreversible renal damage. The use of CyA, therefore, requires a multi-disciplinary approach in which regular consultations and monitoring by a dermatologist and, if warranted, by a nephrologist are imperative.

Introduction

Cyclosporin A (CyA) is a selective immunosuppressant which inhibits the production of interleukin-2 and interferon gamma by T-helper cells. Both these lymphokines play an essential role in the immune response. CyA was first used as an immunosuppressant in 1977 to prevent organ graft rejection. Since then, its efficacy has also been assessed in autoimmune disorders [1] and diseases such as psoriasis vulgaris which have an acknowledged immunological background [2,3]. CyA has the important advantage of being non-myelotoxic as compared to other conventional immunosuppressants.

At present, a review of the up-to-date clinical data on CyA for the treatment of psoriasis vulgaris seems warranted, since this drug offers an important new alternative for treating persistent therapy-resistant skin diseases, and since preliminary results of such therapies appear to be very promising [4-10]. Moreover, CyA in its present galenical formulation, is expected to receive official registration in the near future in Europe for treating severe psoriasis. The drug, however, is not without serious side effects. In this review, various aspects of this new therapy, including the side-effects and drug-interactions in the use of CyA in the treatment of psoriasis vulgaris, are summarized. In addition, appropriate treatment schedules and safety guidelines based on recent data in the literature and our own recent clinical experiences are discussed.

Pharmacokinetics and blood trough-level limits

The pharmacology of CyA was recently reviewed [4].

CyA is insoluble in water. For oral administration (drink solution or capsules), an emulsion based on olive-oil is used as a vehicle. Absorption of CyA varies considerably among individual patients. Generally between 30% and 50% of the administered dose is biologically available. Peak levels of CyA in the blood have been observed between 1 and 8 h (average 3 and 4 h) after intake. The final elimination half-life of the drug is 14-27 h. The drug is generally administered twice daily, taking as a guide, the whole blood trough-level value determined 12 hours after the last intake. Initially, appropriate adjustments in the 12-hourly dose are often necessary to obtain therapeutically effective trough-levels. Optimum trough-levels as determined by radioimmunoassay appear to be in the range of 100-200 ng/ml during chronic administration. If the dose is altered, the new steady state is to be expected after 48 h [5].

It should also be realized that not only too low a dose, but also malresorption in the gut and the concomitant use of certain medicaments which reduce the blood trough-level of CyA could lead to an inadequate therapeutic effect (Table 3, page 19).

Clinical Experiences

The therapeutic potential of CyA in psoriasis was accidently discovered as a side-effect in 1979 when patients with arthritis psoriatica were treated [6]. The first clinical trials were conducted from 1985 once stringent patient selection criteria and strict patient monitoring parameters had been established [7-12]. In these studies the drink solution containing 100 mg/ml in 50 ml bottles was used. Recently the capsules of 100 and 25 mg came available. In open clinical trials, a relatively low dose of about 5 mg/kg/d was observed to have a beneficial therapeutic effect in patients with psoriasis vulgaris [7-10]. This was also confirmed in double-blind studies [11-12].

The remission is dependent on the dose and may vary from 30-35% after about 4 weeks of treatment at a dose of 2.5 mg/kg/d to 75% or higher at a dose of 5 mg/kg/d (Fig. 1), [7,8,13]. After prolonged treatment (for up to 12 weeks), however, a remission of about

60% has been obtained at a dose of 2.5 mg/kg/d (Fig. 1), [14]. Dose-finding studies also indicated that a dose of 5 mg/kg/d or lower was able to maintain the already achieved disease remission at a level which was acceptable to the patient [15,16]. Even during a short therapy period of less than three months (crisis intervention), side-effects such as an increase in blood pressure and in serum creatinine level have been observed [7-12]. However, both these effects were reversible.

Considerable remission was achieved within 8 weeks using an average dose of 3 mg/kg/d CyA in patients who were started off on 1 mg/kg/d CyA, which was increased stepwise until the desired therapeutic effect was achieved [8]. There is no clear consistent correlation between the CyA blood trough-levels and its therapeutic effect in psoriasis [5].

To date, a rebound phenomenon upon termination of CyA-therapy is exceptional [17] and the induction of resistance to CyA (tachyphylaxis) during therapy has not been observed. Relapse (defined as a minimum of 50% return in the activity and the spread of the disease as compared to that observed before therapy) has been observed in all patients after stopping CyA therapy. The period of remission of the disease after discontinuation of CyA is in general unpredictable and may vary from several weeks to months [12]. On average, however, in a subgroup of patients with moderate disease activity, the disease does not relapse any quicker than that observed after discontinuation of photo-chemotherapy (PUVA) or topical therapy with agents such as dithranol [18]. Since topical application of CyA at high concentrations (up to 10%) has no therapeutic effect in psoriasis (see Chapter 6), it has to be given orally [19].

Interactions and side-effects

CyA is extensively metabolized by the cytochrome P-450 system in the liver and excreted via the bile into the feces [20]. Therefore owing to their effect on this cytochrome P-450 system (induction or inhibition), concomitant use of some drugs may reduce or increase the rate of degradation of CyA [20]. This can lead either to sub-therapeutic or to toxic blood trough-levels of CyA at the same dose. An updated list of medicaments that interact with CyA is shown in Table 3, page 19. Drugs that increase the nephrotoxicity of CyA when used concomitantly are also shown in this Table.

The most prominent side-effects of CyA therapy are dose- and time-dependent

nephrotoxicity and hypertension. Additional side-effects which may occur include hyperkalaemia and liver function abnormalities, usually at the beginning of the therapy (average 4%). A reduction in the serum magnesium level has also been reported. Clinically evident side-effects are gingival hyperplasia and hypertrichosis. Subjective side-effects include fatigue, gastrointestinal upsets, tremor, paraesthesias, slight myalgia and transient headaches.

It has been well documented that immunosuppressed patients are at an increased risk for developing malignancies, especially of lymphoreticular origin and, among others, skin carcinomas [21]. However, at the currently recommended blood trough-levels of CyA, the incidence of lymphoproliferative disease is low [21]. The increased potential of PUVA and CyA for the induction of squamous cell carcinomas, in particular, should also be carefully considered [22].

Conditions for treatment

It is essential that a clear agreement on the therapy schedule and on the termination of the therapy is established between the patient and the treating physician. Total withdrawal (or eventual dose reduction) of CyA is warranted if undesirable side-effects occur.

Prior to therapy, an accurate medical history of the patient, especially concerning previous renal disorders, hypertension and medications, should be obtained. Thorough physical and dermatological examinations (including a cervical smear in women) should be performed to exclude any malignancy or infections [21]. Blood pressure should be determined on at least two occasions. It is mandatory to assess the renal function thoroughly at baseline. Serum creatinine levels should be determined twice after fasting and if possible, the glomerular filtration rate (GFR) and the effective renal plasma flow (ERPF) should also be measured. Blood samples should be obtained to determine serum electrolytes (Na, K, Mg), liver function (bilirubin, aminotransferases, alkaline-phosphatase), serum-lipids, blood glucose level, erythrocyte and leukocyte profiles and protein spectrum [11,12,21].

The current absolute and relative contra-indications for the use of CyA are listed in Table I.

Choice of treatment schedule

Possible schedules for optimal treatment can be evaluated on the basis of the activity of the disease prior to therapy and after taking into account the patient's previous experiences regarding the disease. To date, definite treatment schedules with maximum benefit-risk ratios of CyA therapy in different sub-groups of psoriasis vulgaris patients are difficult to establish since relapse of the disease is often unpredictable. In dermatological practice, however, three different basic approaches, as depicted in Fig. 2, may be considered in principle: "short-term treatment", "intermittent treatment" and a treatment for a relatively longer period, "long-term treatment" [13].

A short-term treatment

Short-term treatment has been proposed by us as a safe treatment period varying from 3 to a maximum of 12 months using doses between 2.5-5 mg/kg/d. This regimen has the advantage of achieving an acceptable therapeutic effect within a few weeks with none or minimal and reversible side-effects. The primary aim of the therapy should not be to achieve total remission, but a clinical state that is acceptable to the patient. A dose of about 3 mg/kg/d seems to give the most favorable benefit-risk ratio [8,9,12]. Should there be no improvement after 2 weeks of treatment, the dose may be increased stepwise by 1 mg/kg/d at 2 week intervals up to 5 mg/kg/d. If remission occurs, the dose may be reduced weekly by 0.5-1 mg/kg/d in order to establish the individual minimum effective dose to be able to continue the therapy within the framework of short-term treatment. Monitoring of side-effects is imperative for timely intervention such as dose reduction or total withdrawal of CyA [21,23].

Intermittent treatment

Another possibility is an intermittent treatment schedule whereby the treatment is stopped once the disease has been sufficiently suppressed and is resumed after an interval (Fig. 2) [13,15]. Since, in less extreme active psoriasis, the discontinuation of CyA does not necessarily lead to an immediate relapse of the disease, it is sometimes possible to keep the disease under control by using two therapy periods of several months duration in a year [15,18]. This regime decreases the risk of irreversible renal damage and of a

persistent rise in blood pressure.

Long-term treatment

In chronically active psoriasis of prolonged duration and therapy resistance, in which remission is not easily obtained, discontinuation of CyA could lead to a rapid and severe exacerbation of the disease which is unacceptable to the patient [11]. In such cases, intermittent treatment is not sufficient and a relatively long-term treatment schedule, longer than 12 months (Fig.2), using low dose (maximum 5mg/kg/d) CyA is of considerable therapeutic benefit. If necessary, the treatment may be continued using the minimial effective dose.

This regimen is particularly appropriate for plaque form psoriasis vulgaris. The therapeutic benefit of CyA in other forms of psoriasis has also been reported [24,25].

Monitoring of the patient

Renal Function

As mentioned previously, renal malfunction is one of the most common side-effects of CyA therapy [26-31]. Prolonged uncontrolled treatment with CyA could lead to irreversible renal damage (arteriolopathy, interstitial fibrosis) [31]. It is generally accepted that the occurrence of this side-effect varies markedly among individual patients and depends, among other things, on the dose and on the CyA trough-levels achieved. In order to obtain the maximum therapeutic effect with limited depression in renal function, the blood trough-level should not exceed 200 ng/ml. Native CyA can be determined using specific monoclonal antibody in a radioimmune-assay (RIA) or by high performance liquid chromatography (HPLC) [5].

Prior to therapy, serum creatinine should be determined on two occasions. Determinations of GFR and ERPF values prior to therapy are also recommended since the long-term nephrotoxic effects of CyA therapy in psoriasis are not yet known [28]. Serum creatinine should be determined at 2 week intervals during short-term treatment and repeated at monthly or six-weekly intervals thereafter. If there is a 30% increase in serum creatinine above the patient's baseline value or a 10%-15% reduction in creatinine clearance, the CyA dose should be reduced weekly by 0.5 mg/kg/d until the serum creatinine and/or

creatinine clearance value has returned to baseline. If this does not occur, CyA therapy must be discontinued.

There is a lively discussion as to whether serum creatinine is sensitive enough to indicate the occurrence of renal damage at an early reversible phase [28,29,(see also Chapter 7)] and whether GFR and EPRF determinations are "preferable" or are "strictly indicated". A limited increase in serum creatinine, which does not respond to CyA dose reduction, may be the first indication of irreversible renal damage and, as stated previously, the reason to discontinue therapy.

For all CyA treatment schedules it is "preferable" to check every six months whether the true GFR, determined using inulin or radioisotope, is depressed, since a more or less normal GFR is essential for continuing the therapy, if necessary using a lower dose. In the short-term treatment schedule (< 12 months), if GFR determination is not possible, serum creatinine should be monitored very closely. We consider it to be safe to monitor only this parameter during treatment periods of less than 12 months, because in psoriasis patients treated with CyA at doses of 1-5 mg/kg/d during a mean treatment period of about two years, the depression in GFR and EPRF were reversible [28].

A "sine qua non" for regular intermittent CyA therapy is that in the interval period, both serum creatinine and creatinine clearance values return to baseline. It is preferable to check that both GFR and ERPF, performed 3-4 weeks after the last treatment, have also returned to baseline. When the intermittent treatment schedule is used for several consecutive years, GFR and ERPF, however, are mandatory (Fig. 2).

For continuous long-term treatment (> 12 months) serum creatinine (repeated every 4 - 6 weeks), GFR and ERPF determinations (repeated every 6 months) are mandatory for further safe therapy. This is due to the fact that there is still uncertainty concerning the effect(s) on renal function of a long-term treatment regime possibly continued for several consecutive years.

Blood pressure

CyA therapy often results in increased blood pressure, which in some case can be serious. Blood pressure should be checked at 2-4 week interval. If, in spite of blood pressure reducing therapy with nifedipine (no β-blockers in psoriasis because of increased risk of exacerbation, no diuretics in case of abnormal renal function), the diastolic pressure rises

above 95 mm Hg, or the systolic pressure rises above 160 mm Hg, the dose of CyA should be reduced. If this reduction (0.5 mg/kg/d) has no effect, the therapy should be stopped.

Clinical side-effects

Clinical side-effects such as tremor, gingival hyperplasia and hypertrichosis abate when the dose is reduced. As well as the strict monitoring of blood pressure and of renal function, biochemical parameters should also be evaluated at least at monthly intervals and full blood counts determined at six-month intervals [23]. The risk for possible development of malignancies should be considered particularly during long-term treatment [32].

Combination with other (anti-psoriatic) drugs

The combination of CyA with other anti-psoriatic drugs is still under investigation. For example, addition of retinoids did not convincingly reduce the amount of CyA required [15,33] and combination with PUVA-therapy [34] or methotrexate [35] had no therapeutic benefit. The use of UV radiation brings with it an increased risk of skin tumours. Topical therapies with tar, dithranol or steroid ointments pose no objections.

An interesting new development is that fish oil, in particular the eicosapentanoic acids (EPA) present therein, appear to enhance the clinical effect of CyA [15] and reduce the adverse effect(s) of CyA on renal function. In a recent study, it was shown that psoriasis patients who were treated with both CyA and fish oil showed a marked reduction in renal function abnormalities as compared to those observed in patients who were treated with CyA only. A possible explanation is that the formation of vasoconstrictive arachidonic acid metabolites is inhibited [36]. In a preliminary study [30], the frequency of CyA-associated nephrotoxicity was lower in transplant patients who were treated transdermally with clonidine before and after surgery. The protective effect seemed not to be related to changes in blood pressure. These studies [36,37] have yet to be confirmed.

Conclusions and recommendations

In consultation with the patient, CyA should be reserved exclusively for recalcitrant disabling forms of psoriasis vulgaris. It has yet to be established which treatment schedule is of maximum therapeutic value for each category or sub-groups of severe psoriasis vulgaris patients. Long-term CyA treatment for very severe psoriasis should only be considered if the expected therapeutic benefit outweighs the eventual side-effects. In such cases, close monitoring of blood pressure and renal function is essential. There is no consensus yet on the procedure to follow once CyA therapy becomes contra-indicated and the disease relapses to a level unacceptable to the patient.

It is our opinion that, for the time being, the use of CyA in the present galenical formulation should be confined to dermatology centers that not only have access to expertise in the use of CyA, but also possess the appropriate facilities for monitoring the long-term risks [5]. Treatment of psoriasis patients with CyA requires a multidisciplinary approach in which regular consultations with a dermatologist and if warranted, a nephrologist are imperative.

Future developments should be directed towards new formulations of CyA which have the same efficacy in psoriasis but which spare the kidney.

Table I

Contra-indications for oral cyclosporin A in psoriasis.

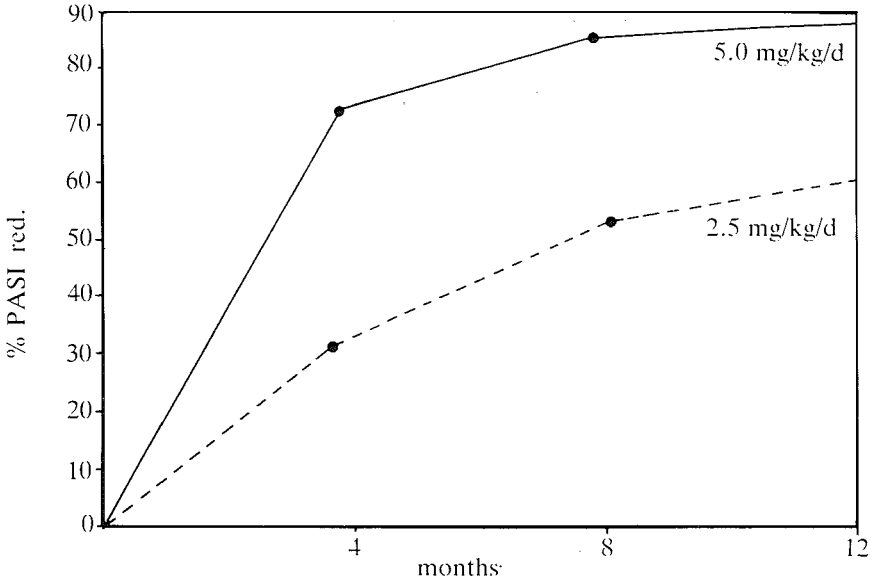
Absolute contra-indications

- Immunocompromized patients.
- Abnormal renal functions.
- Uncontrolable hypertension.
- Acute viral or bacterial infections.
- Pregnancy or lactation.
- History of malignancy.
- Concomitant treatment with nephrotoxic drugs (Table 3, page 19)
- Concomitant treatment with Lovastatine or Simvastatin which predisposes to the occurrence of myopathy.
- Serious side effects of previous cyclosporin A therapy which did not improve upon dose-reduction.
- Hypersensitivity to cyclosporin A.

Relative contra-indications

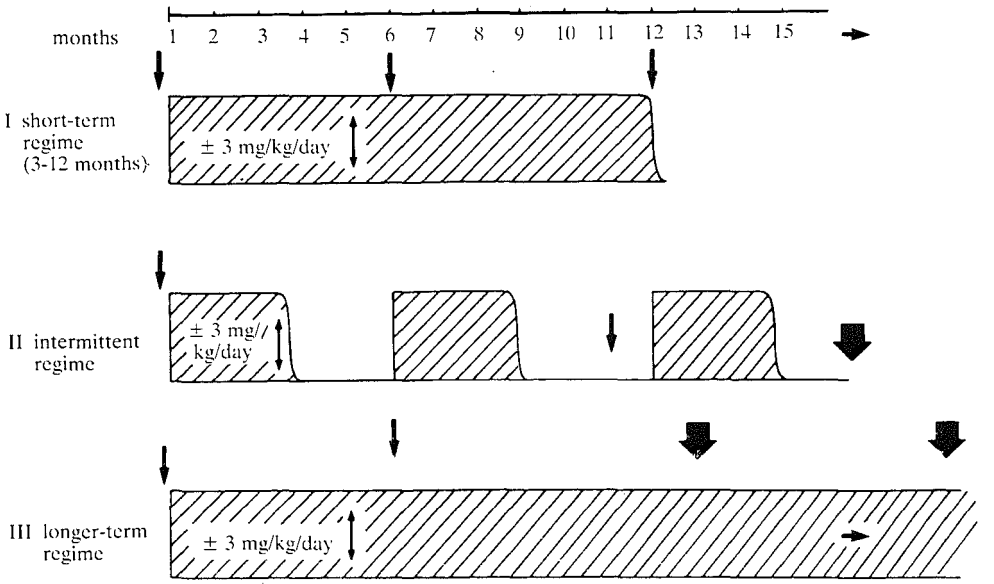
- Limited abnormalities in liver-functions.
- Epilepsy.
- Malabsoption syndrome.
- Drug and/or alcohol addiction.
- Drugs which interfere with the pharmacokinetics of cyclosporin A (Table 3, page 19).
- Previous anti-psoriatic therapies (PUVA, methotrexate, arsenic) which may increase the risk of skin malignancies.

Figure 1.



A comparison between percentage Psoriasis Area and Severity Index (PASI) reduction after the first months of treatment at cyclosporin A doses of 2.5 mg/kg/d and 5 mg/kg/d.

Figure 2.



Schematic representation of three different treatment regimes with cyclosporin A.

↕: Minimal efficacy dose (5 mg/kg/d).

↓: GFR and EPRF "recommended".

⇓: GFR and EPRF "mandatory".

References

1. Bach JF. Cyclosporin in autoimmune diseases. Transplant Proc 1989; 21: 97-113.
2. Valdimarsson H, Baker BS, Jansdottir I et al. Psoriasis: a disease of abnormal keratinocyte proliferation induced by T-lymfocytes. Immunol Today 1986; 7: 256-8.
3. Bos JD. The pathomechanism of psoriasis; The skin immune system and Cyclosporin. Br J Dermatol 1988; 118, 141-55.
4. Meinardi MMHM, Bos JD. Immunopharmacological properties of Ciclosporin in psoriasis. In: Van Joost Th, Heule F, Bos JD (Eds.) Ciclosporin (Sandimmune^{R}) in psoriasis, Actua Sandoz no. 13. Samson Stafleu, Alphen aan de Rijn, The Netherlands 1988: 26-49.
5. Mockli G, Kabra PM, Kurtz TW. Laboratory monitoring of cyclosporine levels: guidelines for the dermatologist. J Am Acad Dermatol 1990; 23: 1275-9.
6. Mueller W, Hermann B. Cyclosporin A for psoriasis. N Engl J Med 1979; 301: 555.
7. Van Joost Th, Heule F, Stolz E et al. Short-term use of Cyclosporin A in severe psoriasis. Br J Dermatol 1986; 114: 615-20.
8. Griffiths CEM, Powles AV, Leonard JN et al. Clearance of psoriasis with low-dose Cyclosporin. Br Med J 1986; 293: 731-2.
9. Marks JM. Cyclosporin A treatment in severe psoriasis. Br J Dermatol 1986; 115: 745-6.
10. Picascia DD, Garden JM, Freinkel RK et al. Treatment of severe psoriasis with systemic Cyclosporin. J Am Acad Dermatol 1987; 17: 408-14.
11. Ellis CN, Gorsulowsky DC, Hamilton TA et al. Ciclosporin improves psoriasis in a double-blind study. JAMA 1986; 256: 3110-6.
12. Van Joost Th, Bos JD, Heule et al. Low-dose Cyclosporin A in severe psoriasis. A double-blind study. Br J Dermatol 1988; 118: 183-90.
13. Van Joost Th, Heule F, Bousema MT. Cyclosporin A in psoriasis. In: Van der Kerkhof PCM, van Vloten WA (eds). Psoriasis, Essex, The Netherlands, ISBN 90-722 93037, 1989; 57-63.
14. Timonen P, Friend D, Abeywickrama K et al. Efficacy of low-dose Cyclosporin A in psoriasis: results of dose-finding studies. Br J Dermatol 1990; 122 (s 36): 33-9.

15. Heule F, Bousema MT, Laeijendecker R et al. Three long-term regimens with Cyclosporin A for psoriasis vulgaris. Acta Derm Venereol (Stockh) 1989; suppl. 146: 171-5.
16. Griffith CEM, Powles AV, McFadden J et al. Long-term ciclosporin for psoriasis. Br J Dermatol 1989; 120: 253-60.
17. Cacoub P. Artru L. Canesi M et al. Lifethreatening psoriasis relapse on withdrawal of Cyclosporin. Lancet 1988; ii 219-20.
18. Higgins E, Munro C, Marks J et al. Relapse rates in moderately severe chronic psoriasis treated with Cyclosporin A. Br J Dermatol 1989; 121: 71-4.
19. Bousema MT, Tank B, Heule F et al. Placebo-controlled study of psoriasis patients treated topically with a 10% Cyclosporine gel. J Am Acad Dermatol 1990; 22: 126-7.
20. Watkins PB. The role of cytochromes P-450 in cyclosporine metabolism. J Am Acad Dermatol 1990; 23: 1301-11.
21. Bos JD, Meinardi MMHM, van Joost Th et al. Use of Cyclosporin in psoriasis. Lancet 1989; ii: 1500-2.
22. Bos JD, Meinardi MMHM. Two distinct skin squamous cell carcinomas in a psoriasis patient receiving low-dose Cyclosporine maintenance treatment. J Am Acad Dermatol 1989; 21: 1305-6.
23. Anonymous. A consensus report: Cyclosporin A therapy for psoriasis. [Editorial] Br J Dermatol 1990; 122 (s 36): 1-3.
24. Meinardi MMHM, Westerhof W, Bos JD. Generalized pustular psoriasis (von Zumbusch) responding to ciclosporin A. Br J Dermatol 1987; 116: 269-70.
25. Gupta AK, Ellis CN, Nickoloff BJ et al. Oral Cyclosporine in the treatment of inflammatory and noninflammatory dermatoses. Arch Dermatol 1990; 126: 339-50.
26. Feutren G, Friend D, Timonen P et al. Predictive value of Cyclosporin A level for efficacy or renal dysfunction in psoriasis. Br J Dermatol 1990; 122 (s 36): 85-93.
27. Mihatsch MJ, Thiel G, Ryffel B. Renal side-effects of Cyclosporin A with special reference to autoimmune diseases. Br J Dermatol 1990; 122 (s 36): 101-15.
28. Powles AV, Carmichael D, Hulme B et al. Renal function after long-term low-dose Cyclosporin for psoriasis. Br J Dermatol 1990; 122: 665-9.
29. Heule F, Wenting GJ, Bousema MT et al. Renal function analysis before, during

and after Cyclosporin A treatment for psoriasis (abstract). Clinical Dermatology in the year 2000, Londen May 1990.

30. Mihatsch MJ, Belghiti D, Bohman SO et al. Kidney biopsies in control or Cyclosporin A-treated psoriatic patients. International Kidney biopsy registry of Cyclosporin A (Sandimmun^{R}) in autoimmune disease. Br J Dermatol 1990; 122 (s 36): 95-100.
31. Barros EJG, Boim MA, Ajzen H et al. Glomerular hemodynamics and hormonal participation on Cyclosporin nephrotoxicity. Kidney Int 1987; 32: 19-25.
32. Cockburn ITR, Krupp P. The risk of neoplasms in patients treated with Cyclosporin A. J Autoimmun 1989; 2: 723-31.
33. Korstanje MJ, van der Staak WJBM. Combination therapy cyclosporin-A-etretinate for psoriasis. Clin Exp Dermatol 1990; 15: 172-3.
34. Korstanje MJ, Hulsmans RFHJ. Combination therapy Cyclosporin A-PUVA in psoriasis. Acta Derm Venereol (Stockh) 1990; 70: 89-92.
35. Korstanje MJ, van Breda-Vriesman CJP, van der Staak WJBM. Cyclosporin A and methotrexate: A dangerous combination. J Am Acad Dermatol 1990; 23: 320-1.
36. Stoof TJ, Korstanje MJ, Bilo HJG et al. Does fish-oil protect renal function in Cyclosporin A treated psoriasis patients (?). J Int Med 1989; 226: 437-41.
37. Luke J, Luke D, Williams LA et al. Prevention of Cyclosporin A-induced nephrotoxicity with transdermal clonidine. Clin Pharmacy 1990; 9: 49-53.

Chapter 9

Summary and conclusions

Summary and conclusions

This thesis deals with the application of cyclosporin A in the treatment of psoriasis.

Chapter 1

In this introductory Chapter the agent cyclosporin A is presented. An outline of its history is given from its discovery in the early seventies to drug of choice for immunosuppression in the majority of organ transplant centres in the world. The pharmacological and immunological properties of cyclosporin A are reviewed. In this respect the blockade of interleukin-2 is explicitly thought to be of major importance. The accidental success in an arthritis patient with psoriasis preluded many investigations in the field of dermatology. Apart from psoriasis a variety of skin disorders were screened for there reaction on cyclosporin A. Finally the known side-effects and drug interactions that limit its use are summarized.

Chapter 2

Different aspects of the skin disease psoriasis are brought forward in this second introductory chapter. The clinical picture is mostly formed by one or more efflorescences such as erythema, scales, papules, plaques or pustules. Histopathology is reviewed with reference to the clinical variability. Apart from genetics, triggering factors, biochemical and especially immunologic aspects are named here as pathomechanisms of psoriasis. The role of T-lymphocytes in the disease process are accentuated. Classical and newer therapy modalities both systemic and topical are named with special attention to their mechanism of action, exclusion criteria and side-effects for a better comparison with cyclosporin A.

Chapter 3

After several anecdotal reports on the effectiveness of cyclosporin A in psoriasis we were the first to treat 5 patients in an open prospective study and put them on 5 mg/kg/d, a lower dose than has been applied in organ transplantation so far. We selected patients with a severe form of psoriasis, resistant to conventional systemic treatment. In 3 patients an almost complete remission was seen and the rest improved considerably within 4

weeks. The mean reduction in the PASI (severity) score was 84%. There was evidence of slight renal dysfunction in one patient. We concluded that cyclosporin A was an effective treatment for the induction of a remission in severe psoriasis (crisis intervention).

Chapter 4

After the breakthrough experience in the pilot study a double-blind protocol was designed to treat 20 patients in the Departments of Dermatology of the University Hospital Dijkzigt and the Academic Medical Center in Amsterdam. In 4 weeks the patients received either low-dose cyclosporin A or placebo and the clinical results appeared to differ significantly. After 4 weeks 8 out of 10 placebo patients switched to active treatment and after another 4 weeks they responded with a 90% reduction in PASI. In an attempt to maintain the remission we tapered the dose stepwise in a 2 months period and in 8 out of 9 patients 3 mg/kg/d were effective. In a post-treatment observation phase 4 out of 5 patients relapsed after a mean interval of 6.5 weeks. Mild hypertension and elevated serum creatinine that occured in some patients were reversible.

Chapter 5

The results of short-term treatment with low-dose cyclosporin A were indeed encouraging but the disease tended to recur after withholding the drug. This was the reason to start a long-term evaluation of three dose regimes. Nineteen patients received either a continuous, an intermittent treatment or a combination of cyclosporin A and the retinoic acid derivative Tigason^{R}. This medicament has a proven antipsoriatic effect but can be hepatotoxic in therapeutic doses (see Chapter 2).

The clinical effects of the continuous and intermittent regime were comparable, the side-effects, however, were less in the latter approach because of a shorter exposition to the drug. In the combination we could not show a beneficial effect surpassing that of each drug given separately (in a low dose) or a cyclosporin A sparing effect.

Chapter 6

The side-effects of cyclosporin A became apparent in the initial high-dose programmes but remained bothersome also in the low-dose treatment protocols, especially nephrotoxicity and hypertension. To avoid these effects topical application seems a promising

solution. In this Chapter the topical use of cyclosporin A in psoriasis, alopecia, contact dermatitis, oral lichen planus and keloid scars is reviewed together with own experiences in some of these dermatological disorders. Apart from the intralesional and swish and spit method, no real clinical effect of topical formulations however, could be noticed. Theoretical considerations and suggestions for further investigations, such as the addition of penetration enhancers, complete this intriguing subject.

Chapter 7

To evaluate the clinical efficacy and safety of two dose regimes 2.5 and 5 mg/kg/d in severe psoriasis a trial had been started with 74 patients in 6 dermatological centers in The Netherlands. The severity and recalcitrant character of these patients' psoriasis is illustrated with the data of their acceptance and reactivity to conventional systemic treatment, such as methotrexate, photo-chemotherapy or retinoids. The 2.5 mg/kg/d dose appeared significantly less effective than the 5 mg/kg/d dose after 4 weeks. This higher dose however, required dose reductions for safety reasons in some 20% of the cases. In this period we analysed cyclosporine A trough levels with a monoclonal RIA kit and found an enormous interindividual variation. Serum creatinine in 4 weeks did not change on 2.5 mg/kg/d but increased 15% with the higher dose. For all the patients, glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) fell about 13%. Additional treatment during at least 12 months with a stepwise dose reduction showed improvement in renal function. In the post-treatment observation phase serum creatinine was not significantly higher than baseline, GFR and ERPF remained under baseline 6 and 8 % respectively. In conclusion serum creatinine is not an ideal filtration marker. For long-term treatment surveillance of renal function is mandatory with GFR or even better ERPF. Intermittent treatment with cyclosporin A alternated with conventional systemic treatment, however, needs further attention.

Chapter 8

The clinical and theoretical "academic" experiences are brought into one frame that can serve as safety guideline for the medical practioner. The pharmacokinetics are summarized in conjunction with blood level estimation of cyclosporin A. A safe level range for parent cyclosporin A is advised in the range of 100-200 ng/ml. For induction of a

remission 5mg/kg/d of cyclosporin A seems insufficient, a start on lower doses can be effective but needs a stepwise increase of the dose. A rebound phenomenon or tachyphylaxis has not been observed. The relapse rate is unpredictable and varies from weeks to months. The interactions with nephro-and hepatotoxic drugs are stressed and the side-effects reviewed. Patient selection criteria and contra-indications are given to prevent disappointing results. The short-term, intermittent and long-term regimes are then outlined together with suggestions for monitoring adverse effects, being mainly renal dysfunctions. Finally combination therapies are discussed, including the vasoprotective effect of fish-oil.

In conclusion the clinical trials with oral cyclosporin A in severe and plaque psoriasis made it obvious that many patients, who suffered from this disabling skin disease really improved on this new oral therapy, mostly in a fast and convenient way. The impact on their lives, personally (improvement of body-image or strenghtening of ego) and as a consequence socially cannot be overestimated. If the safety rules given in detail in this thesis are followed accurately, major problems, especially avoidance of development of structural kidney changes, can be prevented. Both benevolent doctors and demanding patients - in their mutual dependency - have to be aware of the factors that determine the benefit-risk ratio of cyclosporin A therapy. In the future cyclosporin A can thus constitute an important treatment modality, next to conventional regimes such as methotrexate, photo-chemotherapy or retinoids in the immunoregulation of psoriasis variants. In addition the use of cyclosporin A in dermatological diseases can generate still more research that will provide a better insight into the immunomechanisms that are operative in these diseases.

Chapter 10

Samenvatting en conclusies

Hoofdstuk 1

In dit hoofdstuk wordt de stof cyclosporine A geïntroduceerd. Er wordt een overzicht van zijn geschiedenis gegeven vanaf de ontdekking in het begin van de jaren '70 tot aan het moment dat het als eerste keuze geaccepteerd werd voor immunosuppressie in het merendeel van de centra voor orgaantransplantatie in de wereld. De pharmacologische en immunologische eigenschappen van cyclosporine A worden samengevat. In dit opzicht wordt de blokkade van interleukine-2 in het bijzonder van grote betekenis geacht. De behandeling van een patiënt met psoriasis arthropathica waarbij de huidafwijking toevalligerwijs goed reageerde, was een begin van veel onderzoek op het terrein van de dermatologie. Naast psoriasis werden nog bij talrijke andere huidziekten het effect van cyclosporine A onderzocht. Tenslotte worden de nu bekende bijwerkingen en de interacties met geneesmiddelen, die het gebruik beperken, samengevat.

Hoofdstuk 2

Verschillende aspecten van de huidziekte worden in dit tweede inleidende hoofdstuk naar voren gebracht. Het klinisch beeld wordt meestal gevormd door het samengaan van enkele efflorescenties zoals erytheem, schilfering, papels, plaques of pustels. De histopathologie van psoriasis wordt samengevat in samenhang met de klinische wisselvalligheid. Naast genetische factoren worden uitlokkende momenten, biochemische en speciaal immunologische aspecten hier genoemd als de pathomechanismen van psoriasis. De rol van T-lymphocyten in het ziekteproces wordt benadrukt. De klassieke en nieuwere behandelwijzen, zowel systemisch als locaal toegepast, worden op een rij gezet, met speciale aandacht voor hun aangrijpingspunten, exclusie criteria en ongewenste neveneffecten om zo beter te kunnen vergelijken met cyclosporine A.

Hoofdstuk 3

Na enige berichten, steeds een enkele patiënt betreffend, over de werkzaamheid van cyclosporine A bij psoriasis waren wij de eersten die vijf patiënten behandelden in een zogenaamde "open prospectieve studie". Zij werden ingesteld op 5 mg/kg/dag, een lagere dosis dan tot dusver toegepast was bij orgaantransplantaties. Aleen patiënten met een ernstige psoriasis die resistent was tegen in gebruik zijnde systemische behandelwijzen

namen deel. Bij drie patiënten werd een bijna volledige remissie gezien en de rest verbeterde sterk in vier weken tijds. De gemiddelde afname van de graad van ernst, gemeten met de PASI-score was 84%. Er was een aanwijzing voor een lichte nierfunctiestoornis bij één patiënt. We trokken de conclusie, dat cyclosporine A een werkzame behandeling vormde voor het op gang brengen van een remissie bij ernstige psoriasis (crisis interventie).

Hoofdstuk 4

Na de opzienbarende ervaring in de "pilot study" werd een dubbel-blind protocol ontworpen om 20 patiënten te behandelen op de afdeling voor Huidziekten van het Dijkzigt Ziekenhuis te Rotterdam en van het AMC te Amsterdam. Vier weken lang ontvingen patiënten een lage dosis cyclosporine A dan wel een placebo (nepmiddel). De klinische resultaten bleken significant te verschillen. Na verloop van vier weken werden acht van de tien placebo-patiënten overgezet op actieve behandeling. Na nog vier weken hadden zij gereageerd met een PASI vermindering van 90%. In een poging om de remissie te bestendigen, verminderden wij de dosis stapsgewijs in een periode van twee maanden. Bij acht van de negen patiënten was 3 mg/kg/dag nog werkzaam. In een beoordelingsfase, volgend op de behandeling kregen vier van de vijf patiënten opnieuw huidafwijkingen na een gemiddeld tijdsbestek van zes en een halve week. De milde hypertensie en gestegen serum creatinine waarde, die bij enkele patiënten optrad, keerden naar de norm terug.

Hoofdstuk 5

De resultaten van de kortdurende behandeling met een lage dosis cyclosporine A waren inderdaad hoopgevend, maar de ziekte neigde de kop op te steken als het middel werd gestaakt. Dat was de reden om een lange termijn behandeling te starten met het doel drie doseerregimes te vergelijken. Negentien patiënten kregen een continue of een intermitterende behandeling, dan wel een combinatie van cyclosporine A en de van vitamine A zuur afgeleide stof Tigason^{R}. Dit geneesmiddel heeft een bewezen antipsoriatische werking, maar het kan leverbeschadiging geven in de werkzame dosis (zie Hoofdstuk 2). Het klinisch effect van het continue en intermitterend beleid was vergelijkbaar. De nevenverschijnselen evenwel waren bij de laatste variant minder tengevolge van de

kortere tijd dat de patiënt aan het middel had blootgestaan. Bij de combinatiebehandeling konden wij geen positief effect aantonen dat sterker was dan het effect van elk middel afzonderlijk - en in lage dosering - of een cyclosporine A sparend effect.

Hoofdstuk 6

De neveneffecten van cyclosporine A werden duidelijk in de oorspronkelijke behandelschema's met een hoge dosering, maar bleven ook hinderlijk in de schema's die uitgingen van een lagere dosering, met name nierbeschadiging en hypertensie. De toepassing òp de huid of slijmvliezen lijkt een veelbelovende oplossing om deze invloeden te vermijden. In dit hoofdstuk wordt een overzicht gegeven van de locale toepassing van cyclosporine A bij psoriasis, alopecia, contact eczeem, orale lichen planus en keloidale littekenreacties, tezamen met onze eigen ervaringen met enkele van deze huidziekten. Uitgezonderd de intralesionale en "mondspoel-en-spuw" methode, kon echter van de locale toedieningsvorm geen werkelijk klinisch effect worden opgemerkt. Theoretische overwegingen en suggesties voor verder onderzoek, zoals het gebruik van penetratieversnellers, vormen het besluit van dit intrigerende onderwerp.

Hoofdstuk 7

Om het klinisch effect en de veiligheid van twee doseerschema's te vergelijken, n.l. 2,5 en 5 mg/kg/dag, werd een onderzoek gestart met 74 patiënten in zes dermatologische centra in Nederland. De ernst en het therapie-resistente karakter van de psoriasis van deze patiënten wordt toegelicht met de gegevens over de acceptatie en de reactie op de gebruikelijke systemische behandeling, zoals methotrexaat, photochemotherapie of retinoïden. De 2,5 mg/kg/dag dosis bleek significant minder werkzaam dan de 5 mg/kg-/dag dosis na vier weken. Deze hogere dosis echter behoefde reductie uit veiligheidsoverwegingen in ongeveer 20% van de gevallen. In deze periode analyseerden wij de cyclosporine A dalspiegels met een monoclonale RIA kit en vonden sterk wisselende interindividuele waarden. Het serum creatinine niveau veranderde in vier weken op 2,5 mg/kg/dag niet, maar steeg 15% onder invloed van de hogere dosis. Bij al de patiënten daalden de glomerulair filtratie snelheid (GFR) en de effectieve renale plasma flow (ERPF) ongeveer 13%. Onder voortgezette behandeling gedurende tenminste twaalf maanden, met een stapsgewijze vermindering van de dosis, werd een verbetering van de

nierfunctie zichtbaar. In de controleperiode na de behandeling was het serum creatinine gehalte niet significant hoger dan de uitgangswaarde. De GFR en de ERPF bleven resp. 6 en 8% onder de uitgangswaarde.
Samenvattend kan gesteld worden, dat de serum creatinine waarde geen ideale maat is voor de filtratie. Kortom tijdens een langdurige behandeling is de bewaking van de nierfunctie noodzakelijk door middel van de GFR of nog beter door de ERPF. Een intermitterende behandeling met cyclosporine A, afgewisseld met een gebruikelijk systemische behandelwijze, verdient uit veiligheidsoverwegingen alle aandacht.

Hoofdstuk 8

De klinische en theoretische "academische" ervaringen worden nu in een raamwerk gebracht, dat kan dienen als veiligheidsvoorschrift voor de medicus practicus. De pharmacokinetiek wordt samengevat in samenhang met bloedspiegelbepalingen van cyclosporine A. Als veilige grenzen voor het cyclosporine A zelf, zonder metabolieten, wordt geadviseerd om 100-200 ng/ml aan te houden. Om een remissie te bewerkstelligen lijkt 5 mg/kg/dag voldoende. Beginnen met een lagere dosis kan werkzaam zijn, maar behoeft een stapsgewijs ophogen van de dosering. Een zogenaamd rebound verschijnsel en tachyphylaxie worden niet waargenomen. De snelheid waarmee de huidafwijkingen opnieuw terugkeren is onvoorspelbaar en wisselt van weken tot maanden. De interacties met nier-en leverbeschadigende geneesmiddelen worden benadrukt en de neveneffecten worden op een rij gezet. De criteria voor de selectie van patiënten en de contra-indicaties worden gegeven om teleurstellende resultaten te voorkomen. Vervolgens worden de korte termijn, de intermitterende en de lange termijn regimes besproken, tezamen met aanbevelingen om het ontstaan van neveneffecten te bewaken, met name nierfunctieverlies. Tenslotte worden combinatietherapieën, inclusief het beschermend effect van visolie op de bloedvaten, van commentaar voorzien.
Samenvattend kan gesteld worden, dat de klinische onderzoekprogramma's met cyclosporine A bij het ernstige ziektebeeld van de psoriasis en plaque ons geleerd hebben dat vele patiënten, die gebukt gingen onder de zo ernstig invaliderende ziekte, werkelijk verbeterden op deze nieuwe orale therapie en meestal op een snelle en gemakkelijke manier. De invloed op hun leven, persoonlijk - door een verbetering van hun lichaamsbeeld of de versterking van hun ego - en dientengevolge sociaal, kan niet overschat worden. Als de

veiligheidsnormen, die in dit proefschrift in detail zijn gegeven, zorgvuldig worden nagevolgd, kunnen grote problemen, in het bijzonder de ontwikkeling van structurele nierbeschadiging, voorkomen worden. Welwillende dokters evengoed als mondige patiënten, dienen - in hun wederzijdse afhankelijkheid - zich bewust te zijn van de factoren die het evenwicht van voor-en nadelen van een cyclosporine A therapie bepalen. Aldus kan cyclosporine A in de toekomst een belangrijke behandelmogelijkheid vormen naast in zwang zijnde regimes zoals methotrexaat, photochemotherapie of retinoïden. Bovendien zal het gebruik van cyclosporine A bij huidziekten nog meer onderzoek op gang brengen, dat een beter inzicht kan verschaffen in de immunologische mechanismen, die in deze ziektebeelden werkzaam zijn.

ADDENDUM 1 **PASI scoring list**

Project	Center No.	VISIT 3	Patient No. ☐ ☐☐☐
Sandimmune®			Initials ☐☐
in therapy resistant plaque type psoriasis			Date of exam. ☐☐ ☐☐ ☐☐ Day Month Year
Investigator		WEEK 1	

Psoriasis Area and Severity Index (PASI)

Scoring system

Score	0	1	2	3	4	5	6
Erythema Infiltration Desquamation	none	slight	moderate	severe	very severe	——	——
Area %	0	<10	10<30	30<50	50<70	70<90	90–100

HEAD (H)

	Score
Erythema	☐
Infiltration	☐
Desquamation	☐
Sum	☐☐
x Area	☐
=	☐☐
x 0,1 =	☐☐☐

TRUNK (T)

	Score
Erythema	☐
Infiltration	☐
Desquamation	☐
Sum	☐☐
x Area	☐
=	☐☐
x 0,3=	☐☐☐

UPPER LIMBS (UL)

	Score
Erythema	☐
Infiltration	☐
Desquamation	☐
Sum	☐☐
x Area	☐
=	☐☐
x 0,2 =	☐☐☐

LOWER LIMBS (LL)

	Score
Erythema	☐
Infiltration	☐
Desquamation	☐
Sum	☐☐
x Area	☐
=	☐☐
x 0,4=	☐☐☐

PASI = (H)+(T)+(UL)+(LL)= ☐☐☐ + ☐☐☐ + ☐☐☐ + ☐☐☐ = ☐☐☐

Frederiksson T
Petterson U
Dermatologica 1978; 157: 238-44

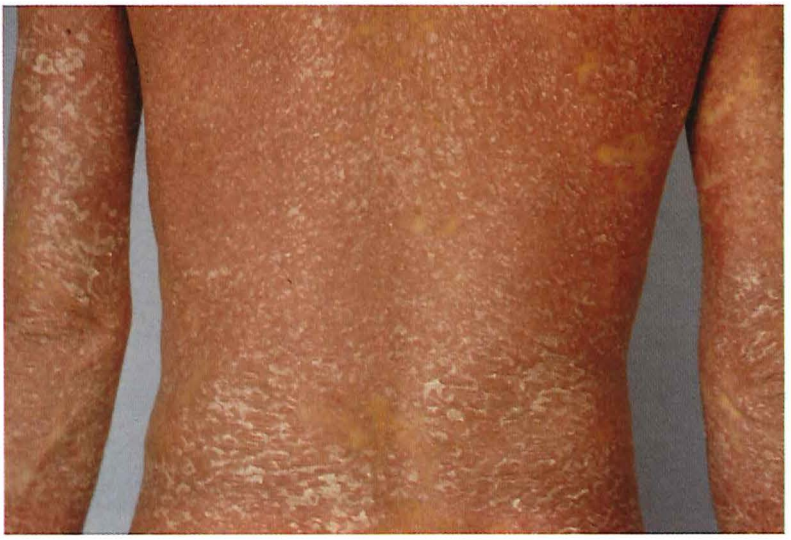


Plate 1. Trunk. Psoriasis vulgaris, before cyclosporin A treatment

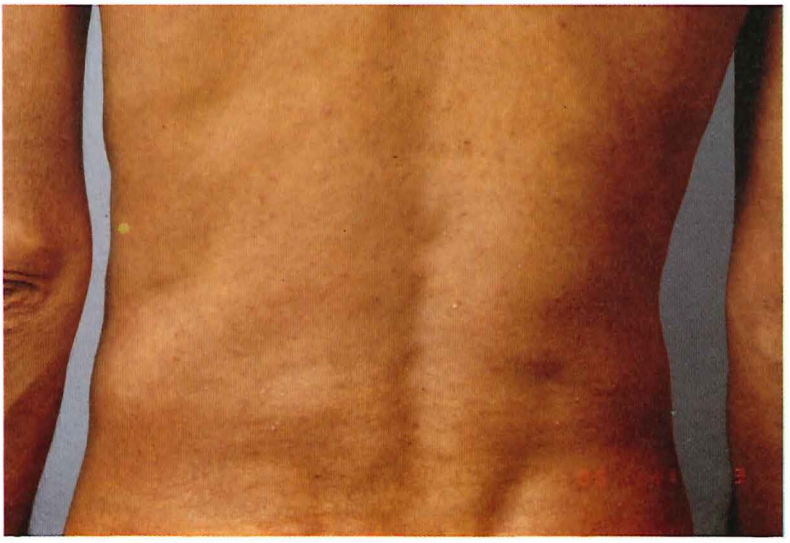


Plate 2. Trunk. Psoriasis vulgaris, after 4 weeks cyclosporin A treatment

Colour Plates

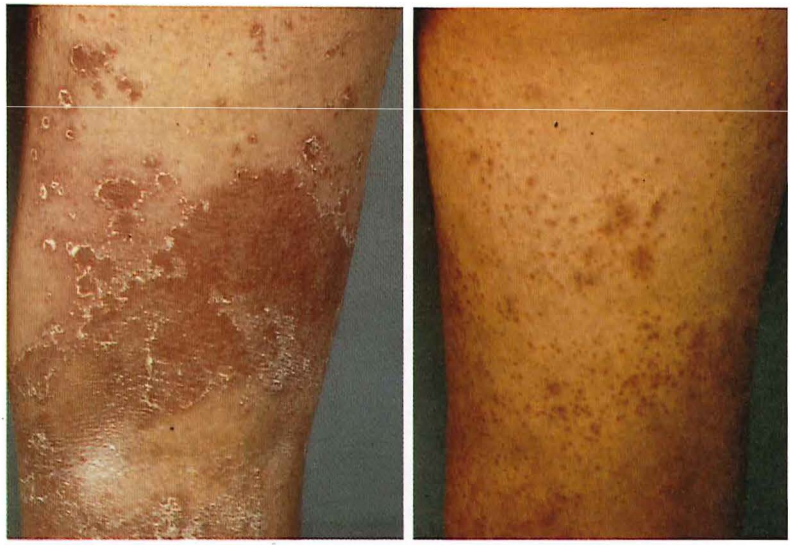


Plate 3. Upper leg left. Psoriasis vulgaris, before treatment
Right. Mild relapse 3 weeks after withdrawal of cyclosporin A treatment

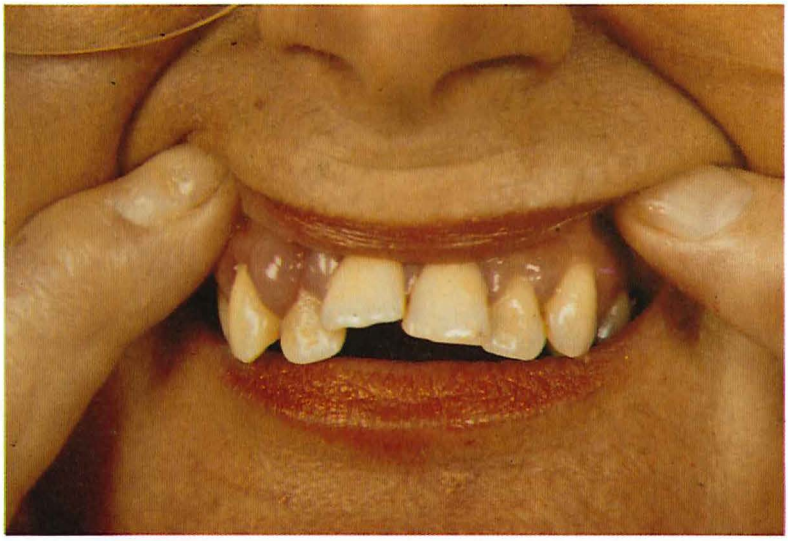


Plate 4. Mouth. Side-effect of cyclosporin A treatment:
Gingiva Hyperplasia. After 6 weeks

Colour Plates

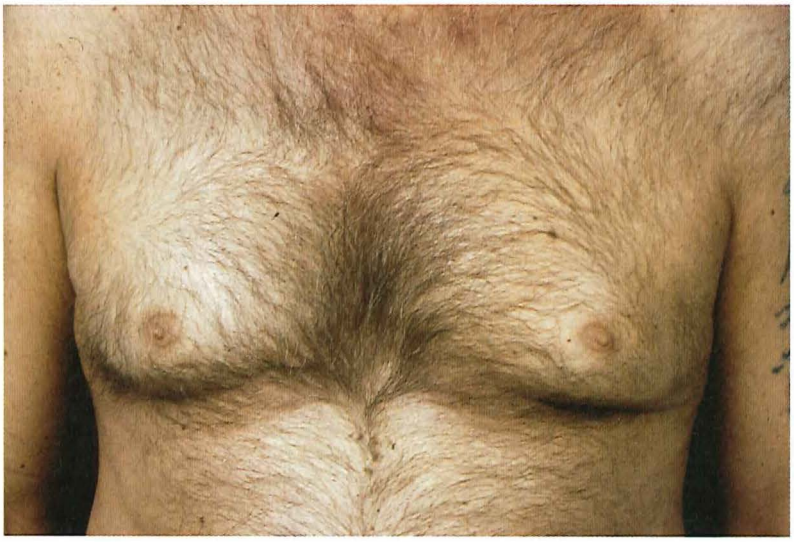


Plate 5. Trunk. Before cyclosporin A treatment. Psoriasis elsewhere on the body

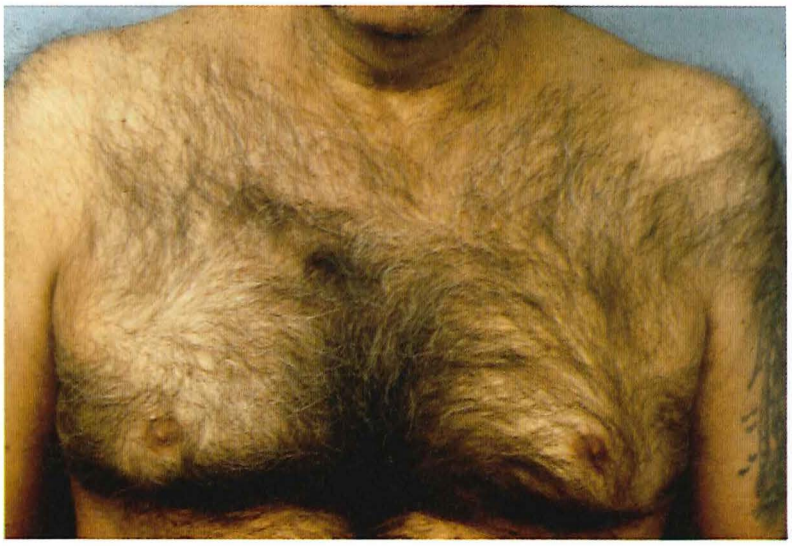


Plate 6. Trunk. Side-effect of cyclosporin A treatment
Hypertrichosis. After 6 weeks

Colour Plates

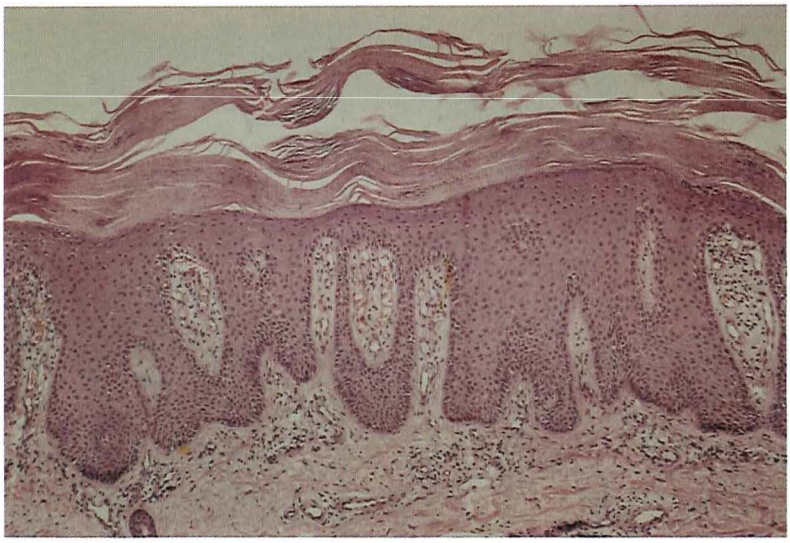


Plate 7. Histopathology of a psoriasis lesion. Haematoxylin-eosin staining

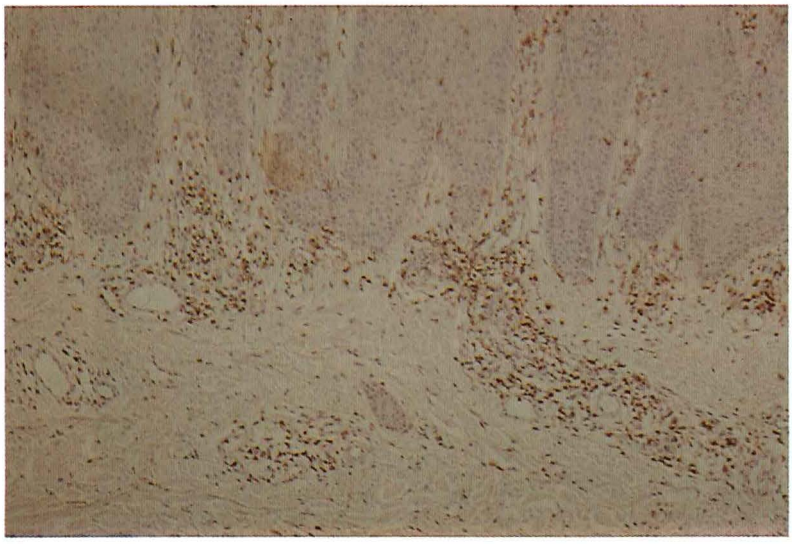


Plate 8. Same section as Plate 7. Staining with anti-Leu 3a monoclonal antibodies shows dermal infiltrate consisting of T helper lymphocytes.

Addendum 3

List of abbreviations

APC	antigen presenting cell
BFC	blister fluid concentration
BP	blood pressure
BW	body weight
CARA	chronic a-specific respiratory disease
C_{cr}	creatinine clearance calculated with Cockcroft's formula
Ci	Curie
CRABP	cellular retinoid binding protein
CyA	cyclosporin A
D	Dalton
DMSO	dimethylsulphoxide
DNFB	dinitro fluorbenzene
DTH	delayed type hypersensitivity
E	exacerbation
EDTA	edetic acid
EGF	epidermal growth factor
EPA	eicosa pentanoic acids
ERPF	effective renal plasma flow
F	failure
FA	fumaric acid
FNA	formularium Nederlandse Apothekers
FPIA	fluorescence-polarization immuno assay
GFR	glomerular filtration rate
HLA	human leucocyte antigen
HPLC	high performance liquid chromatography
ICAM	intercellular adhesion molecule
IFN	interferon
IgE	immunoglobulin E

IL	interleukin
INH	isoniazide
IP	initial PASI
iv	intravenous
LFA	lymphocyte function associated antigen
M	maintenance
MTX	methotrexate
NSAID	non steroid anti-inflammatory drug
ODC	ornithine decarboxylase
PAF	platelet activating factor
PASI	psoriasis area and severity index
PMNL	polymorphonuclear leucocyte
PUVA	psoralen and UV-A or photo-chemotherapy
re-PUVA	retinoids combined with PUVA
RI	remission induction
RIA	radioimmunoassay
SRT	signed rank test
TPA	tumor promoting phorbol ester
UV	ultraviolet light

Dankwoord

Het in dit proefschrift beschreven onderzoek werd grotendeels verricht op de kliniek en polikliniek van de afdeling Dermatologie en Venereologie van het Academisch Ziekenhuis Dijkzigt te Rotterdam (Hoofden: Prof. dr. Th. van Joost en Prof. dr. E. Stolz).

Velen die op enigerlei wijze hebben bijgedragen aan de totstandkoming van dit proefschrift wil ik hartelijk danken.

Enkelen wil ik in het bijzonder noemen.

Prof. dr. Th. van Joost, die mij, direct na mijn aanstelling de gelegenheid gaf om te participeren in de onderzoeksactiviteiten. Beste Theo, dank dat je mij de ruimte gaf om een sterk klinisch accent aan de studie te geven. Aan de vele stimulerende gesprekken denk ik met genoegen terug.

Dr. G.J. Wenting, Gert-Jan, hartelijk dank voor je inzet met de medewerkers van de afdeling Nephrologie, voor de kritische bewaking van de "gezonde" populatie patiënten, die we exposeerden aan cyclosporine A. Je magisch realisme bij het totstandkomen van Hoofdstuk 7 bewonder ik.

De leden van de promotiecommissie, Prof. dr. R. Benner, Prof. dr. P.R. Saxena en Prof. dr. M.A.D.H. Schalekamp noem ik gaarne omdat ze dit proefschrift becommentariëerden.

Dr. J.W.O. van der Berg en zijn laboratoriummedewerkers dank ik voor de talloze cyclosporine-spiegel bepalingen en technische adviezen dienaangaande, evenals Dr. Th. Stijnen van de afdeling Biostatistiek van de Erasmus Universiteit, die deels in samenwerking met Drs. A. Bosman waardevolle adviezen gaf voor de bewerking van een vloed van getallen.

Mijn dank gaat ook naar de collegae dermatologen in de participerende ziekenhuizen van Amsterdam (VU), Heerlen, Maastricht, Helmond en Den Haag. Het regelmatig overleg was zakelijk en productief, maar had telkens toch een persoonlijk (en culinair) cachet. Speciaal wil ik in dit verband noemen de samenwerking met de afdeling Dermatologie van het Academisch Medisch Centrum te Amsterdam (Hoofd Prof. dr. J.D. Bos).

Dr. B. Tank dank ik voor de zorgvuldige controle van de Engelse tekst en talloze praktische suggesties, evenals mevrouw H.H. de Klerk-Teule, die de Nederlandse tekst corrigeerde.

Dr. V.D. Vuzevski van de afdeling Klinische Pathologie, dank voor de plezierige afhandeling van al mijn bioptmateriaal en verrijking van mijn kennis op het gebied van de histopathologie.

Vele collega's op de Afdeling Dermatologie hebben het mede mogelijk gemaakt dit proefschrift te schrijven. In het bijzonder Dr. Ben Naafs, chef de policlinique en de arts-assistenten Ronald Laeijendecker en Mente Bousema, inmiddels dermatoloog, hebben veel werk verzet.

Voor de technische assistentie dank ik mevrouw Wil Voermans, die de tekst nog eens helemaal uitgetypt heeft en samen met de heer Hans Moes de lay-out voor haar rekening nam, alsook de heer Johan van der Stek, die het fotowerk verzorgde en mevrouw Joke Pepermans, die de grafieken tekende.

Voor de bereidwilligheid om mee te werken aan de onderzoeken ben ik al de patiënten zeer erkentelijk. Zij bleven trouw, mede dankzij de aandacht en zorg van de verpleging van de kliniek (Hoofd: Zr. L. Agerbeek) en de polikliniek (Hoofd: Zr. M.G. Kenswil) en hun medewerkers. Zonder de nauwgezette monitoring van de trials en de steun van de firma Sandoz, in het bijzonder van de heer J. Stokvis had ik dit werk niet kunnen doen.

Allen die mij fysiek op de been hielden tijdens deze excercitie, ook al liep alles ogenschijnlijk op rolletjes ben ik zeer dankbaar.

Tenslotte dank ik jullie, mijn lieve vrouw en jongens, voor het geduld dat jullie hebben opgebracht in de periode dat ik "aan een vlaag van wetenschap leed".

Ter nagedachtenis aan Prof. dr. G.L. Kalsbeek

Curriculum vitae of F. Heule

15-02-1948	Born in Amsterdam
09-03-1979	Physician's degree, Vrije Universiteit Amsterdam
12-03-1979 until 04-07-1980	Assistant physician, Department of Lung diseases, Military Hospital "Dr. A. Mathijsen" Utrecht
01-09-1980 until 01-09-1984	Training for specialist in dermatology and venereology at the department of dermatology, University of Utrecht.
01-01-1985	Appointment as Chef de Clinique at the department of Dermatology and Venereology, University Hospital Dijkzigt, Rotterdam