Different aspects of psoriasis etiology and treatment

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To my family

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ABSTRACT

Psoriasis is a chronic disease where treatments are often needed throughout life. The quality of life of patients is often affected and comorbidities are common. The overall aim of this thesis was to study treatment regimes, assessments and comorbidity in psoriasis patients with the intention of finding treatment strategies that work in daily practice and improves patients' quality of life.

In Paper I, bacterial and fungal cultures were studied from intertriginous areas in psoriasis patients with and without topical steroid treatment and from healthy controls. The results show that untreated psoriatic patients were colonised by *Staphylococcus aureus* significantly more often than the control group but infection seemed to be unlikely. *Candida* was not found in any of the groups. We propose that intertriginous psoriasis could be treated with topical steroids alone.
In Paper II, the effectiveness, quality of life and side-effects were compared between the treatments with methotrexate and ciclosporin. The mean PASI change from baseline at 12 weeks was 58% in the methotrexate group and 72% in the ciclosporin group, showing ciclosporin to be more effective than methotrexate. The improvement of the VAS score was also higher in the ciclosporin group.
In Paper III, the sub-analysis of the assessment tools used in the second study showed that the VAS correlated with the PASI and the DLQI, except at the baseline visit for the PASI. We suggest that the VAS could be used to assess disease activity and quality of life for psoriasis patients in everyday clinical practice.
In Paper IV, the experience and risk of dental caries and periodontal disease were assessed in psoriasis patients and controls, and similar profiles were observed in the two groups.

Conclusion: Intertriginous psoriasis can be treated with topical steroids alone. Ciclosporin is more effective than methotrexate from a short-term perspective, although methotrexate also gives a satisfactory effect and is safer from a long-time perspective. The VAS method for assessing disease activity and quality of life in psoriasis can be recommended. In psoriasis patients, no overall increased risk for dental caries and periodontal disease was demonstrated.

Keywords: Psoriasis, *Staphylococcus aureus*, *Candida*, Methotrexate, Ciclosporin, Dermatology Life Quality Index, Psoriasis Area and Severity Index, Visual Analogue Scale, obesity, dental caries, periodontal disease

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I. Flytström I, Bergbrant IM, Bråred J, Brandberg LL. Microorganisms in Intertriginous Psoriasis: No Evidence of *Candida*. Acta Derm Venereol. 2003; 83(2):121-123.

II. Flytström I, Stenberg B, Svensson A, Bergbrant IM. Methotrexate vs. ciclosporin in psoriasis: effectiveness, quality of life and safety. A randomized controlled trial. Br J Dermatol. 2008; 158(1):116-121.

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IV. Fadel H, Flytström I, Calander AM, Bergbrant IM, Heijl L, Birkhed D. Profiles of dental caries and periodontal disease experience and risk in patients with psoriasis. Submitted for publication.

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ABBREVIATIONS

AE	Adverse event
APC	Antigen presenting cell
BB-UVB	Broad-band ultraviolet B
BCC	Basal cell carcinoma
BMI	Body mass index
BoP	Bleeding on probing
BP	Bodily pain
BSA	Body surface area
CASPAR	Classification criteria for psoriatic arthritis
CCL	Chemokine ligand
CD	Crohn´s disease
CRP	C-reactive protein
DC	Dendritic cell
DMFS	Decayed, missing or filled tooth surfaces
DLQI	Dermatology life quality index
ESR	Erythrocyte sedimentation rate
GH	General health
GM-CSF	Granulocyte/macrophage colony stimulating factor
HDL	High density lipoprotein
HLA	Human leukocyte antigen
IFN	Interferon
IL	Interleukin
MH	Mental health
MHC	Major histocompatibility complex
NAFLD	Non-alcoholic fatty liver disease
NB-UVB	Narrow-band ultraviolet B
n.s.	Not significant
PASI	Psoriasis Area and Severity Index
PAQ	Psoriatic and arthritis questionnaire
PF	Physical functioning
PIIINP	Procollagen III n-terminal propeptide
PPD	Probing pocket depth
PsA	Psoriasis arthritis
PSORS	Psoriasis susceptibility locus
PUVA	Psoralen + ultraviolet A
QoL	Quality of life
RCT	Randomized controlled trial
RE	Role emotional
RF	Rheumatoid factor
RP	Role physical

SCC	Squamous cell carcinoma
SF	Social functioning
SF-36	Short form-36
TCR	T cell receptor
Th cell	T helper cell
TNF	Tumour necrosis factor
UC	Ulcerative colitis
UV	Ultraviolet
VAS	Visual analogue scale
VT	Vitality

1 INTRODUCTION

1.1 Psoriasis

1.1.1 Epidemiology

Psoriasis is found worldwide, affecting approximately 1% to 3% of the population. Men and women are equally affected. Psoriasis exhibits a bimodal distribution with a peak between 15 and 20 years of age and another peak between 55 and 60 years. (1; 2) On the basis of the bimodal distribution of the age at onset and inheritance, two types of psoriasis have been discussed. Type I psoriasis (approximately 65% of the psoriasis population) is associated with onset below the age of 40, a positive family history of psoriasis, a preceding streptococcal sore throat, and guttate lesions. Type II psoriasis (35% of psoriasis patients) appears to be associated with a population with onset after the age of 40 years and with no family history of psoriasis. Type II is not linked to a preceding infectious trigger. The dominate clinical picture is chronic plaques and an association with nail and joint involvement has been described. (3)

1.1.2 Clinical features

There are several psoriasis phenotypes. The most common clinical variant is psoriasis vulgaris, which affects approximately 85 to 90% of all patients with the disease. Psoriasis vulgaris (*Figure 1*) is characterised by raised, well-demarcated, erythematous plaques with adherent silvery scale. The areas that are affected the most are the elbows, knees, sacral region and scalp. Other predilection sites include hands, feet, nails and the intertriginous areas (groins, axilla, umbilicus, crena ani, retroauricular folds). (4) The psoriasis plaques in intertriginous areas are characterised by an oozing, red inflammation without scaling. The true incidence of intertriginous psoriasis is unknown. In a study by Farber et al. (5) it was found that 44 % of the psoriasis patients had perianal involvement, and in a Swedish study by Inerot et al. (6), it was found that the anogenital area was affected in 24 % of the

patients. Other clinical variants of psoriasis are guttate, erythrodermic and pustular. Each form can coexist or interchange with other forms.

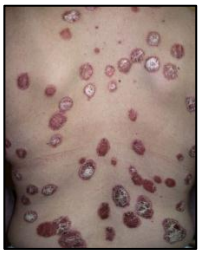
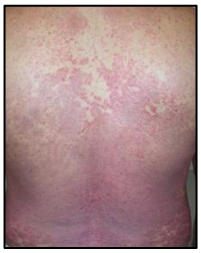
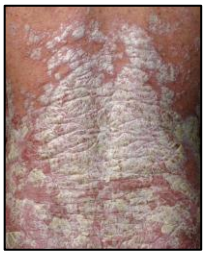
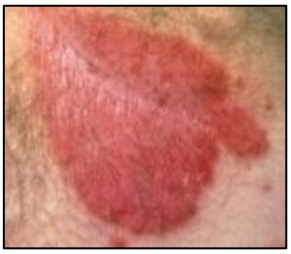





Figure 1. Plaque psoriasis *Intertriginous psoriasis*
Photo: A. Inerot

1.1.3 Histological features

The psoriasis scales are a result of a hyperproliferative epidermis with premature keratinocyte maturation and incomplete cornification with retention of nuclei within the cells of the stratum corneum (parakeratosis). The mitotic rate of the basal keratinocytes is increased and causes thickening of the epidermis. The redness of the lesions is due to increased numbers of tortuous capillaries that reach the skin surface. There is an immune cell infiltrate composed of dendritic cells and CD4+ Th cells within the upper papillary dermis, and neutrophils and CD8+ Th cells within the epidermis. (7) Neutrophilic granulocytes form characteristic Munro's microabscesses.

1.1.4 Immunopathogenesis

The pathogenesis of psoriasis is a complex interaction among genetic, immunological, and environmental components. It was previously assumed that Th1 cells played the dominant role in the initiation and maintenance of psoriasis but, in recent years, the view has changed in favour of a Th17 mediated disease. Innate immune cells produce key cytokines (TNF-α, IFN-α, IFN-γ, IL-1β, and IL-6) that activate dendritic cells. Activated dendritic cells present antigens and secrete mediators such as IL-12 and IL-23, leading to the differentiation of Th1 and Th17. IL-23 serves as a key master cytokine regulator. T cells secrete mediators (e.g., IL-17 and IL-22) that activate keratinocytes and induce the production of antimicrobial peptides, proinflammatory cytokines and chemokines. These mediators feed back into the proinflammatory disease cycle and shape the inflammatory infiltrate. (8)

1.1.5 Genetics

The mode of inheritance of psoriasis is complex. Several susceptibility loci for psoriasis vulgaris (*PSORS*) have been identified, but the major genetic determinant of psoriasis is *PSORS1*, which is located within the major histocompatibility complex (MHC) on chromosome 6p. Current data suggest that HLA-Cw6 is the susceptibility allele within *PSORS1*. This association is particularly strong in patients with early onset psoriasis. (9) One of the most important features of HLA-C is its capacity to regulate both innate and adaptive responses at the levels of both antigen presentation and natural killer cell regulation. (10)

1.1.6 Environmental triggers

Psoriasis can be provoked or exacerbated by a variety of different environmental factors, particularly infections and drugs. Streptococcal infection is strongly associated with guttate psoriasis. In a study of Mallbris et al. (11) , acute streptococcal pharyngitis was verified in 63% of the patients with guttate phenotype at disease onset. The use of various drugs such as lithium, β-blockers, angiotensin-converting enzyme inhibitors, antimalarial agents and IFN-α has also been associated with induction or deterioration of the disease. (12)

Severe acute mental stress can also precede the debut of psoriasis. (11) Smoking has been discussed as a risk factor for psoriasis. Several studies have shown a link between psoriasis and cigarette smoking; patients with psoriasis are at least twice as likely to smoke cigarettes than the general population, and occasional reports have shown that smoking has a negative effect on psoriasis. (13; 14; 15) Heavy tobacco intake also confers an increased risk of more clinically severe disease. (16) Physical trauma (e.g. surgical incisions and tattoos) can give rise to the Koebner phenomenon. (17) The Koebner phenomenon constitutes psoriasis plaques that form at the site of a skin injury, and usually occurs within one to two weeks of injury to the dermis.

1.1.7 Microorganisms

Various microorganisms have been associated with the provocation and/or exacerbation of psoriasis. Certain strains of *Staphylococcus aureus* can

produce enterotoxin and one theory is that exacerbation of psoriatic lesions is most likely mediated via toxin secretion. (18) The enterotoxins are highly potent activators of T cells. Due to the ability of the staphylococcal enterotoxins to activate a high frequency of T cells, they have been designated as Superantigens. Superantigens simultaneously bind to MHC class II on APCs and to the TCR on T cells. This cross-linking of APCs and T cells results in a polyclonal activation of $CD4^+$ and $CD8^+$ T cells. This leads to a massive T cell proliferation and an excessive production of cytokines. (19).

It is well-known that β-hemolytic streptococci (Group A, C and G) isolated from the tonsils, are associated with both acute and chronic forms of psoriasis. (20; 21) Leung et al. (22) reported cutaneous infection with *Candida albicans* in association with the exacerbation of skin lesions. Although the role of the *Malassezia* species in psoriasis has yet to be determined, they may play an important role, especially in psoriasis involving the scalp, eyebrows, ears and seborrhoeic areas of the trunk. (23; 24)

Normal, healthy skin is colonised by *S. aureus* in 5 - 30% compared with approximately 60% of patients with psoriasis. (18; 25; 26) β-hemolytic streptococci group A ,C and G are rarely seen in normal skin. Gram-negative bacteria make up a small proportion of the skin flora, mostly in moist intertriginous areas and not on dry skin. (27) *C. albicans* colonises the skin, genital mucosa and/or intestinal mucosa of 30–70% of healthy individuals at any given time and, under normal circumstances, the fungus does not cause significant disease. (28; 29) The *Malassezia* species are part of the resident skin flora. *Malassezia* occur mainly in areas rich in sebaceous glands such as the chest, back, and scalp.

1.2 Assessment tools

In clinical trials, a large variety of assessment tools have been used to evaluate the severity of psoriasis, but there is a lack of standardisation. (30) In recent years, the introduction of quality of life instruments has improved psoriasis evaluation, but there is a need for consensus in order to make valid comparisons between studies. (31) In a review article it was found that in randomised controlled trials, the Psoriasis Area and Severity Index (PASI) was the most commonly used measure to describe the extent of psoriasis and

the Dermatology Life Quality Index (DLQI) was the most common tool for measuring quality of life. (32)

1.2.1 Psoriasis Area and Severity Index

The Psoriasis Area and Severity Index (PASI) is a widely used tool for the measurement of the severity of psoriasis**.** (33) The PASI combines the assessment of the severity of lesions and the area affected, into a single score within the range of 0 to 72. The body is divided into four sections: head (10% of the body area), arms (20%), trunk (30%) and legs (40%). Each of these areas is scored separately, and the four scores are then combined. For each section, the percentage of the area of skin involved is estimated and then transformed into a grade from 0 to 6. The PASI is the most validated objective method to measure the severity of psoriasis (34) and has a high intra-rater reliability and a good interobserver correlation when used by trained assessors. (35) The PASI system is sensitive to changes and reflects disease improvement or deterioration, although the sensitivity to change for small areas of involvement is poor. (36; 37) PASI 75 is a widely used concept, meaning the percentage of patients achieving a 75% improvement in PASI from baseline to the primary endpoint, usually 12 to 16 weeks of treatment. Achieving a 75% improvement in the PASI is considered to be successful treatment. PASI 50 (50% improvement) and PASI 90 (90% improvement) are sometimes also used.

1.2.2 Body Surface Area

The Body Surface Area (BSA) is an instrument to estimate the extent of psoriasis involvement, calculating one palm of the hand represent 1% of the total body surface area. (36; 38) The advantages of BSA are that it is quick and convenient to use, with a low test-retest variability for the same observer. However, there is moderately high interrater variability and the method is likely to overestimate the extent of psoriatic lesions. (39; 40)

1.2.3 Dermatology Life Quality Index

The Dermatology Life Quality Index (DLQI) is a ten-item questionnaire evaluating the quality of life in patients with dermatological diseases. (41) It consists of six subscales: symptoms and feelings, daily activities, leisure,

work and school, personal relationships and treatment satisfaction. The DLQI can give a total score of 30 with a higher score indicating a poorer quality of life. An estimate of the minimal clinically important difference of the DLQI total score is a 5 point improvement. (42) However, if patients score less than 5 points at baseline, the definition of a clinically meaningful response is expanded to include patients who achieved a DLQI total score of 0. (43) A set of intervals of DLQI scores is proposed: 0-1=no effect at all on patient's quality of life, 2-5=small effect, 6-10=moderate effect, 11-20=very considerable effect and 21-30=extremely substantial effect. The reliability and validity of the DLQI is well-established. (41; 44; 45)

1.2.4 Short Form -36

The Short Form-36 (SF-36) is a general health status instrument and includes one multi-item scale that is applicable to research, general population surveys and health policy evaluations. The SF-36 is used in clinical trials and has shown good reliability and validity for psoriasis. (44; 46; 47) The SF-36 is divided into physical health, subdivided into physical functioning (PF), role-physical (RP), bodily pain (BP), general health (GH) and into mental health subdivided into vitality (VT), social functioning (SF), role-emotional (RE) and mental health (MH). The SF-36 consists of eight scaled scores, which are the weighted sums of the questions in their section. Each scale is directly transformed into a 0-100 scale on the assumption that each question carries equal weight.

1.2.5 Visual Analogue Scale

The Visual Analogue Scale (VAS) is a 100-millimetre horizontal line with descriptive phrases representing extremes of sensation placed at either end. The subject places a mark on the 100 mm line at the most appropriate point. (48) The VAS is a tool that is often used to measure subjective phenomena. It has shown a high level of reliability (49) and validity in terms of assessing pain. (50) The VAS has previously been used in different psoriasis studies, mainly to reflect the intensity of itching (51; 52; 53) and in one study it was also used to measure the patient's self-assessment of the severity of his/her psoriasis and its impact on quality of life. (54)

1.3 Treatment

1.3.1 Treatment goals

The treatment strategy is based on disease severity. The European consensus states the definition of disease severity and treatment goals for psoriasis. (55) Mild psoriasis is defined as BSA ≤10, PASI ≤10 and DLQI ≤10. Moderate to severe psoriasis is defined as BSA >10 or PASI >10 and DLQI >10. Treatment goals (assessed after 10-16 weeks) are a reduction of PASI ≥75% and DLQI 0 or 1. (56) If a treatment regimen results in a reduction of PASI ≥75% or PASI ≥50% to <75% combined with a DLQI ≤5, treatment is successful and therapy should be continued. When there is a reduction in PASI <50% or PASI ≥50% to <75% combined with a DLQI >5, treatment modifications should be considered, including increasing the drug dose, reducing intervals between drug doses, combining therapies or changing the drug. (55)

1.3.2 Treatment options

The recommended treatment for mild psoriasis is to start with topical therapy and move to phototherapy or systemic treatment in refractory cases. For moderate to severe psoriasis, phototherapy or systemic therapies are recommended.

1.3.2.1 Topical treatment

1.3.2.1.1 Emollients

Emollients are used to soften scaling and reduce irritation. The treatment has a positive effect on skin hydration and acts as a barrier function in psoriasis patients. (57)

1.3.2.1.2 Corticosteroids

Corticosteroids have an anti-inflammatory and immunomodulating effect. Corticosteroids inhibit different proinflammatory cytokines such as TNF-α. (58; 59) Corticosteroids with a low to mild potency are used for intertriginous

psoriasis and face lesions. Potent and super potent corticosteroids are used on the body and the scalp. There has been concern regarding the long-term use of corticosteroids. Side-effects that may occur include cutaneous atrophy and the development of striae. (60; 61) There is also a possibility of hypothalamic–pituitary–adrenal axis suppression occurring with prolonged use of excessive quantities of corticosteroids. (62)

1.3.2.1.3 Calcipotriol

Calcipotriol is a vitamin D analogue affecting epidermal proliferation and differentiation. (63) Calcipotriol is used for plaque psoriasis. Calcipotriol in a fixed combination with betamethasone dipropionate has a faster onset of action than monotherapy (64) Calcipotriol can cause irritant reactions. (60)

1.3.2.1.4 Calcineurin inhibitor

Tacrolimus and pimecrolimus are immunomodulating agents (58) and can be used for the treatment of intertriginous and facial psoriasis. (65; 66) The main side effect is local burning. The long-term knowledge concerning a possible risk of developing skin cancer on areas exposed to the sun is limited.

1.3.2.2 Phototherapy

1.3.2.2.1 Ultraviolet B

The mechanism of action of Ultraviolet B (UVB) treatment is not fully understood. The number of epidermal T lymphocytes and dendritic cells (DCs) decrease and there is a reduction in keratinocyte proliferation. (67; 68) UVB treatment is a standard treatment for moderate to severe plaque psoriasis and guttate psoriasis. The former use of broad-band UVB (BB-UVB) (290–320 nm) is now often replaced by narrow-band UVB (NB-UVB) **(**311±2 nm). The most common side effects of UVB therapy are erythema and burning. BB-UVB is not thought to lead to a risk of developing skin cancer (69; 70), but the risk of NB-UVB is under debate. No significant association between NB-UVB treatment and BCC, SCC or melanoma has yet been seen, but ongoing risk assessments are essential. (71)

1.3.2.2.2 Psoralen + Ultraviolet A

PUVA treatment is psoralen (oral or bath) in combination with Ultraviolet A (320-400 nm). Psoralen is a compound in a family of natural products known as furocoumarins. Psoralen intercalates into the DNA and, on exposure to ultraviolet UVA radiation, form covalent interstrand cross-links with thymine, inducing apoptosis. Exposure to more than 350 oral PUVA treatments greatly increases the risk of developing squamous cell carcinoma (SCC) (72) and PUVA treatment has therefore declined over the past few years. However, no risk of developing skin cancer has been seen with bath-PUVA treatment. (73; 74)

1.3.2.2.3 Climate therapy

Sun exposure has an immunomodulating effect with local and systemic reduction of T cells and cytokines. (75) Climatotherapy is the oldest form of phototherapy.

1.3.2.2.4 Grenz rays

The exact mechanism of action of Grenz rays (Bucky) is unknown but it has effects on the Langerhans cells in the epidermis. (76) Grenz rays have wavelengths of around 20 nm, lying between x-rays and ultraviolet rays. Grenz rays are used mainly for scalp psoriasis, but also for psoriasis in the intertriginous areas and for hand and foot psoriasis. Side effects are erythema and hyperpigmentation. One concern is skin malignancy, but the risk is considered to be low if the cumulative dose is less than 100 Gray. (77)

1.3.2.3 Traditional systemic treatment

1.3.2.3.1 Methotrexate

Methotrexate is a synthetic folic acid analogue with anti-proliferative and anti-inflammatory properties. (78) Polyglutamate, which is the primary metabolite in methotrexate, competitively inhibits dihyrofolate reductase, preventing the reduction of folate cofactors. This results in preventing pyrimidine and purine synthesis and DNA methylation. Methotrexate empties the intracellular stores of activated folate. Cell replication is disrupted and this leads to the inhibition of epidermal cell proliferation. (79) At low doses, methotrexate has potent anti-inflammatory actions that appear to be mediated via pathways that are separate from folate antagonism. The inhibition of polyamines is thought to contribute to its anti-inflammatory effects. (80) Methotrexate is the first line treatment for moderate to severe psoriasis when systemic treatment is needed. Methotrexate can be administered orally, subcutaneously or intramuscularly. Two different dosage regimes have been proposed. A single, once-weekly dose and a triple dosage schedule given at 12-hours intervals, with the latter regimen based upon cell cycle kinetic studies. (81) The two dosing schedules seem to be equally effective, and a single once-weekly dose is the most commonly used regime today. Parenteral administration is advocated when there is gastrointestinal intolerance. Significant variation is seen in the bioavailability of oral methotrexate. (82) There is conflicting evidence as to whether the bioavailability of methotrexate is affected by the presence of food, with some denying (83) and others confirming a decrease in absorption. (84) Gastrointestinal complaints are the most common side effects and are often dose dependent and may be minimised by folic acid administration. (85) Folate supplements are also used to lessen the risk for severe side effects such as liver toxicity and mylelosuppression. (86; 87) The risk of liver fibrosis/cirrhosis in methotrexate treatment is higher in psoriasis patients with diabetes, obesity and who consume significant amounts of alcohol. (86; 88) Fibrotic changes can occur in the presence of normal liver enzymes, (89) which is why other assessments are needed. The standard procedure used earlier was to take liver biopsies, but the benefit of serial liver biopsies has been questioned. In recent years biopsies have to a large extent been replaced

by a non-invasive method, procollagen III N-terminal propeptide (PIIINP). (90)

1.3.2.3.2 Ciclosporin

Ciclosporin is a cyclic polypeptide consisting of eleven amino acids. It suppresses the activation of the calcium-dependent phosphatase calcineurin, inhibiting lymphokine secretion (e.g.,IL-2, IFN- γ, GM-CSF, IL-3, IL-4, TNF-α and IL-17) which leads to diminished activation of T lymphocytes. Ciclosporin also inhibits antigen presenting cells. (91; 92; 93) Ciclosporin is used for severe psoriasis. In recent years, the use has diminished since the introduction of biologic therapies. However, it does still have its place when there is a need for a rapid effect. Ciclosporin is nephrotoxic and functional kidney damage can occur quickly after treatment has started. With intermittent treatments, the kidney function can be normalised between treatment periods. The risk of irreversible kidney damage increases during long-term treatment (more than two years) or ciclosporin doses of >5 mg/kg per day (94; 95) Hypertension is another side effect, but is reversible after reducing the dose or after starting antihypertensive treatment. (96) Ciclosporin treated patients who were previously given high doses of UV and especially PUVA, are at greater risk of developing skin malignancy, especially SCC. (97; 98; 99)

1.3.2.3.3 Acitretin

Acitretin is a retinoid (synthetic vitamin A derivate) and has antiproliferative and immunomodulatory properties. In the epidermis, acitretin reduces the proliferative activity and favours the differentiation of epidermal keratinocytes. Acitretin inhibits the induction of Th17 cells and promotes the differentiation of T-regulatory cells. (100) Acitretin is used for plaque psoriasis (especially in combination with UVB and PUVA) and also for pustulous psoriasis, hyperkeratotic hand- and foot psoriasis and erythrodermia. Side effects are mainly hyperlipidemia and elevated liver enzymes. (101)

1.3.2.4 Biologics

Biologics are drugs derived from living material and that interfere with the immune system. Biologic therapies for psoriasis were introduced in Sweden in 2004. They are used for the treatment of moderate to severe psoriasis when traditional systemic therapies are contraindicated or cannot be used due to side effects or have not led to satisfactory treatment result. (102) There is a greater risk of developing serious infections during treatment, and screening for tuberculosis and hepatitis is mandatory before treatment starts. To date, there is no robust evidence of an increase in the risk of malignancy, but a possible future risk of lymphoma or other malignancies cannot be ruled out.

1.3.2.4.1 Etanercept

Etanercept is a human soluble TNF receptor fusion protein, binding free circulating TNF-α which competitively blocks TNF-α to bind to TNF-receptors. It is administered through subcutaneous injections. (103)

1.3.2.4.2 Adalimumab

Adalimumab is a fully human anti TNF- α monoclonal antibody and it is administered through subcutaneous injections. (104)

1.3.2.4.3 Infliximab

Infliximab is a chimeric human-mouse antibody that binds to both soluble TNFα and TNFα on the cell wall and is administered through intravenous infusions. (105)

1.3.2.4.4 Ustekinumab

Ustekinumab is a human monoclonal antibody that binds with high affinity and specificity to the p40 protein subunit that is used by both the interleukin (IL)-12 and the IL-23 cytokines. It is administered through subcutaneous injections. (106)

1.4 Comorbidity

Psoriasis is associated with several comorbidities, including psoriatic arthritis, metabolic syndrome and cardiovascular disease, gastrointestinal and liver disease, malignancy and depression. It has been suggested that the immune-mediated chronic inflammatory processes are a contributing and potentially independent risk factor for certain comorbidities associated with psoriasis.

1.4.1 Psoriatic arthritis

The most well-known comorbidity in patients with psoriasis is psoriatic arthritis (PsA), with a prevalence of 10–30%. (107; 108) PsA is characterised by the development of pain, swelling, and tenderness of the joints surrounding ligaments and tendons. PsA can progress to an erosive, polyarticular disease with joint destruction and loss of functionality (i.e. arthritis mutilans). Skin disease typically presents before arthritis in more than 80% of the patients, and psoriasis symptoms usually precede joint symptoms by an average of 10 years. (109; 110) PsA is equally common in men and women, and the onset of the disease is usually between 30 and 55 years of age. PsA is classified according to the CASPAR criteria. (111)

1.4.2 Metabolic syndrome

Metabolic syndrome is frequently seen in patients with psoriasis. (112) Metabolic syndrome can be defined as central obesity and the presence of two or more of the components: 1. Raised triglycerides or history of treatment for this lipid abnormality, 2. Reduced HDL cholesterol or history of treatment for this lipid abnormality, 3. Raised blood pressure or treatment of previously diagnosed hypertension, 4. Raised fasting glucose level or previously diagnosed type 2 diabetes mellitus. (113) Obesity is a common comorbidity of psoriasis, and multiple studies have demonstrated that patients with psoriasis are more frequently overweight (BMI≥25) or obese (BMI≥30) compared with patients without psoriasis. It has been demonstrated that a higher BMI coincides with a greater degree of psoriasis disease severity. (13;

15; 114) Obese individuals exhibit many symptoms of chronic low-grade inflammation. Although the causal nature of the relation between psoriasis and obesity remains unclear, a process mediated by proinflammatory cytokines derived from Th1 cells is common to both psoriasis and obesity, and is considered to be crucial to the underlying pathogenesis of these two conditions. (115; 116) However, new findings indicate that obesity selectively promotes expansion of the Th17 T-cell lineage. IL-17A mediates many important interactions between adipose tissue and the immune system and new studies suggest that IL-17A is expressed at elevated levels in obese individuals, as it is in psoriasis patients. (117)

1.4.3 Cardiovascular disease

Patients with severe psoriasis are at greater risk of developing cardiovascular disease. (118) Systemic inflammation has been associated with the development of atherosclerosis (119) which suggests that psoriatic patients may be at greater risk of developing cardiovascular disease. Studies report that plasma acute-phase protein levels (C-reactive protein, fibrinogen, and plasminogen activator inhibitor-1) were significantly elevated in patients with psoriasis compared with healthy controls. (120; 121) Elevation in the levels of C-reactive protein is emerging as a risk factor for cardiovascular disease and has been shown to be predictive of cardiovascular disease in healthy patients. (122) In a study by Strober et al., (123) C-reactive protein levels in patients with psoriasis (with or without psoriatic arthritis) indicated an intermediate to high risk of developing cardiovascular disease. A number of epidemiologic studies have also suggested that patients with psoriasis are at greater risk of developing myocardial infarction independently of other established risk factors (124; 125) but this finding remains controversial. (126; 127)

1.4.4 Gastrointestinal disease and liver disease

The prevalence of gastrointestinal disease and non-alcoholic fatty liver disease (NAFLD) is greater in psoriasis patients. The prevalence in psoriasis patients compared to the general population for NAFLD is 48-59% / 20-30%, Crohn's disease (CD) 0.5% / 0.004-0.04%, ulcerative colitis (UC) 0.5% / 0.05-0.07% and for celiac disease 0.2–4.3% / 1%. The magnitude of the association with psoriasis seems to be greater for CD compared with UC.

(128) Psoriasis and CD are inflammatory disorders primarily mediated by Th1 lymphocytes producing cytokines such as TNF-α and IFN-γ. In recent years, an important role for Th17 cells has also been found, in CD as well as in psoriasis. (129) NAFLD includes conditions ranging from relatively benign fatty liver to non-alcoholic steatohepatitis, fibrosis, cirrhosis, and eventually hepatocarcinoma. The metabolic syndrome is associated with both psoriasis and NAFLD. (130) Gisondi et al. (131) found that NAFLD was associated with the severity of psoriasis independently of potential confounders such as age, gender, body mass index, psoriasis duration, and alcohol consumption. Miele et al. (132) found NAFLD to be unrelated to psoriasis severity, but revealed that psoriatic patients with NAFLD were much more likely to have psoriatic arthritis.

1.4.5 Malignancy

Psoriasis is associated with an increased risk of malignancy, although the supporting data is inconsistent. The risk increase is greatest for patients with severe psoriasis treated with systemic therapies and minimal or no risk at all, for patients with milder disease. The increased risk is mainly for lymphoproliferative cancers and nonmelanoma skin cancers (133). However, defining the contribution of psoriasis to the cause of lymphomas is a complicated matter since these diseases are rare. The risk of psoriatic patients developing lymphoid malignancies, may be attributable to the pathophysiology and also to the treatment of psoriasis. (133; 134) In addition to lymphoma and non-melanoma skin cancers, psoriatic patients are at greater risk of developing other malignancies, including those of the head and neck, solid organs (liver, pancreas, lung, breast, kidney), and genitals. (135; 136)

1.4.6 Psychiatric disease

Moderate to severe psoriasis is associated with marked physical and psychological morbidity, with up to 40% of patients reporting that their disease has negative effects on their ability to daily function. (137) High anxiety scores have been reported in over one-third of the psoriatic patients (138) and clinical depression in as many as 60%. (139) There also appears to be an association between psoriasis and lifestyle choices that can have a negative impact on the general health of patients, which can contribute directly to both medical and psychological comorbidities.

1.4.7 Oral disease

Dental cavities and periodontal (gum) disease are the most common oral diseases. Dental caries is a major oral health problem in most industrialised countries, affecting 60-90% of schoolchildren and the vast majority of adults. Severe periodontitis, which may result in tooth loss, is found in 5-20% of middle-aged adults. Oral diseases share common risk factors with chronic diseases such as cardiovascular disease, cancer, chronic respiratory disease and diabetes. Smoking is a major risk factor for adult periodontal disease and other risk factors are unhealthy diet (sugar), excessive consumption of alcohol and poor oral hygiene. (140)

Intraoral psoriatic lesions are relatively uncommon and can affect the buccal mucosa, palate and gingiva. Lesions can manifest as yellow to white borders, frank ulcerations and desquamative gingivitis, and be asymptomatic or with tenderness and a burning sensation. There also appears to be an increase in the frequency of geographic tongue and fissured tongue in patients with psoriasis. (141; 142; 143)

2 AIMS OF THE INVESTIGATION

The studies included in this thesis cover selected aspects regarding treatment regimes, assessments and comorbidity, with the aim of finding treatment strategies that work in daily practice and improve the quality of life for psoriasis patients.

Paper I

The aim was to investigate the occurrence of microorganisms in skinfolds affected by psoriasis and the influence of topical treatment.

Paper II

The aim was to compare two traditional systemic psoriasis treatments (methotrexate and ciclosporin) with respect to effectiveness, quality of life and side-effects, in a way that reflected ordinary clinical routines in dermatological clinics in Sweden.

Paper III

This study compared the VAS instrument with the most commonly used instruments for measuring psoriasis severity and quality of life, with the aim of finding a simple method to follow patient reported treatment outcome.

Paper IV

The aim was to assess the experience and risk of dental caries and periodontal disease in psoriatic patients compared with controls.

3 SUBJECTS AND METHODS

3.1 Subjects

3.1.1 Paper I

In this cross-sectional study, intertriginous areas were cultured for bacteria and fungi in thirty-seven patients with intertriginous psoriasis and nineteen control subjects whose skin folds were not affected. The patients and controls were selected consecutively at the Department of Dermatology, Sahlgrenska University Hospital in Gothenburg between 1995 and 2000.

Three groups were studied:

1. Untreated group: 32 psoriasis patients with no topical treatment in the intertriginous areas for at least 2 weeks prior to inclusion. 18 males and 14 females, mean age 61 years.
2. Treated group: 13 psoriasis patients treated with topical steroids. Five males and eight females, mean age 60 years. 10 patients treated with group II steroid (clobetasone butyrate) and 3 patients with group III steroid (mometasone furoase).
3. Control group: 19 control subjects whose skinfolds were not affected. 8 males and 11 females, mean age 62 years.

Exclusion criteria:

- Systemic or topical antimicrobial treatment within 2 weeks prior to enrolment.
- UV treatment within 2 weeks prior to enrolment.

3.1.2 Paper II

In this multicenter randomised controlled trial, eighty-four patients with chronic plaque psoriasis, eighteen years of age or older, were randomised on a 1: 1 basis to receive either methotrexate or ciclosporin for 12 weeks. Randomisation was performed with the use of computer-generated random numbers, and the investigators received the randomisation numbers by calling a central telephone number. The psoriasis patients were recruited from the Departments of Dermatology at Sahlgrenska University Hospital in Gothenburg (53 patients), at Umeå University Hospital (13 patients), at Malmö University Hospital (5 patients) and at the Departments of Dermatology in Borås (10 patients) and Karlskrona (2 patients). In the initial phase of the study, the Department of Dermatology in Skövde was participating (1 randomised but excluded patient), but the Department then withdrew its further participation in the study). The patients recruited to the study were either patients usually attending the departments or patients who responded to an advertisement in the local daily newspapers. The inclusion periods were between 2002 and 2005.

Inclusion criteria:

- Men or women ≥ 18 years
- Moderate to severe chronic plaque psoriasis
- Insufficient response to topical treatment and/or UV-treatment

Exclusion criteria:

- UV treatment within 2 weeks of randomisation
- Treatment with methotrexate, ciclosporin or acitretin within 4 weeks of randomisation
- Liver or renal impairment
- Untreated or uncontrolled hypertension (>160/95)
- Haematological disease
- Previous or ongoing malignancy
- Immunosuppression due to disease or treatment (inhalation steroids or per oral steroids < 10 mg/day accepted)
- Medication contraindicated by methotrexate or ciclosporin
- Previous or ongoing alcohol or drug abuse
- Planned or ongoing pregnancy or breastfeeding
- Noncompliance

The treatment regime in the methotrexate group was to start with an initial dose of 7.5 mg weekly, given according to the Weinstein and Frost schedule. (81) If the response was inadequate (<50% reduction of PASI score) and no considerable adverse effects were recorded, the dose was to be gradually increased to a maximum of 15 mg weekly. 5 mg folic acid was given daily except on the methotrexate days. The treatment regime in the ciclosporin group was to start with an initial dose of 3 mg/kg per day (divided into two doses) and was to be increased to a maximum of 5 mg/kg per day, according to the same criteria as for methotrexate.

3.1.3 Paper III

This study was a subanalysis of the assessment tools (VAS, PASI and DLQI) used in the randomised controlled trial (Paper II). Data from the 68 psoriasis patients receiving either methotrexate or ciclosporin was collected. The assessment tools were compared without any analysis between the groups.

3.1.4 Paper IV

In this cross-sectional case-control study, 165 men and women (psoriasis patients and controls) were recruited from the Department of Dermatology, Sahlgrenska University Hospital in Gothenburg between 2008 and 2010. The psoriasis patients and controls (visiting the Dermatology department for a diagnosis other than psoriasis) were responding to an advertisement that was visible in the waiting room at the Department of Dermatology. The control group also comprised hospital personnel and relatives/friends of the psoriasis patients. All the subjects attended the Dermatology and the Odontology Departments and psoriasis patients also attended the Rheumatology Department.

Inclusion criteria psoriatic patients:

- Men or women ≥ 40 years
- Psoriasis ≥ 10 years
- History or visible signs of psoriasis

Inclusion criteria control persons:

- Men or women ≥ 40 years
- No history of or presence of psoriasis

3.2 Methods

3.2.1 Microbiological techniques (Papers I and IV)

Paper I

Samples for bacterial and fungal cultures were taken from intertriginous areas in psoriasis patients and controls. The bacterial culture medias used were Colombia agar medium and a selective agar medium for Gram-negative rods, streptococci and staphylococci. Sabouraud's glucose medium and Casein medium containing thiamine were used for fungal cultures.

Paper IV

Counts of two salivary cariogenic bacteria, mutans streptococci and lactobacilli were determined on selective agar media.

3.2.2 Biochemistry (Papers II and IV)

Laboratory tests performed in Papers II and IV included blood count, serum creatinine, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, bilirubin, urine analysis, cholesterol and triglycerides. Additional tests in Paper II included assays of electrolytes, PIIINP, magnesium, albumin and ciclosporin concentration and in Paper IV, Rheumatoid factor (RF), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and blood glucose.

3.2.3 Assessments

3.2.3.1 PASI (Papers II, III and IV)

The PASI was the primary outcome measure in Paper II. Blinded assessors performed the PASI at baseline and monthly thereafter. To minimise inter-rater and intra-rater discrepancy, all assessors underwent a 2-day special training course before the start of the study.

In Paper III, the PASI was compared to the DLQI and the VAS.

In Paper IV, the PASI was one of the methods used to assess the psoriasis severity at the dermatology visit.

3.2.3.2 BSA (Paper IV)

The BSA was one of the methods used to assess the psoriasis severity at the dermatology visit.

3.2.3.3 VAS (Papers II, III and IV)

In Paper II, patients were asked to record the degree of disease activity ranging from zero (no complaints) to 100 (worst complaints) at the VAS. The VAS was used at baseline and after 4, 8 and 12 weeks of treatment. The question asked to the patient was: "What is your experience of your psoriasis today?"

In Paper III, the VAS instrument was compared with the PASI and the DLQI.

In Paper IV, the patients were using the VAS to record the degree of discomfort from any present oral lesions.

3.2.3.4 DLQI (Papers II and III)

In Paper II, the DLQI was one of the of the secondary outcome measures for measuring quality of life. The patients completed the DLQI at baseline and after 8 and 12 weeks.

In Paper III, the DLQI instrument was compared with the VAS and the PASI.

3.2.3.5 SF-36 (Paper II)

In Paper II, the SF-36 was one of the secondary outcome measures for measuring quality of life and the patients completed the SF-36 at baseline and after 8 and 12 weeks.

3.2.4 Rheumatological examination (Paper IV)

At the Department of Rheumatology, the psoriasis patients answered the psoriatic and arthritis questionnaire (PAQ), which is a form containing 10 questions about joint stiffness, swollen joints, back troubles, finger and toe nails, suspected or known arthritis and family history of arthritis. (144) The rheumatologist used the CASPAR criteria to classify PsA. (111) To satisfy the CASPAR criteria, a subject had to have inflammatory articular disease in either joint, spine or entheses with at least 3 points from the following features: current psoriasis (scores 2 points), a personal or family history of psoriasis if no current psoriasis, nail dystrophy, negative RF, dactylitis and juxta-articular new bone formation.

3.2.5 Dental examination (Paper IV)

At the Department of Odontology, the patients and controls were examined by the dentist, who did not know whether or not the subjects had psoriasis. Four bitewing radiographs were taken to assess approximal caries and the alveolar bone level in the posterior region. Unstimulated and paraffin-stimulated whole saliva samples were collected to determine secretion rate and buffer capacity. An oral examination was performed and dental caries, probing pocket depth and the number of remaining teeth were registered.

3.3 Ethical considerations

Papers II and III were approved by the Medical Products Agency in Sweden and by the medical ethics committee at each centre. Papers I and IV were approved by the local ethics committee at the University of Gothenburg

3.4 Statistics

3.4.1 Paper I

A statistical analysis was performed using Fisher's exact test (two-tailed) for comparison of independent samples.

3.4.2 Paper II

When calculating sample size we decided that a clinically interesting difference between the two treatment regimens would occur when one produced a mean reduction in PASI of 75% and the other of only 50%. A clinically interesting difference between treatments was found with 35 patients in each treatment group when the power was set at 0.90 and the significance level at 0.05. Tests between groups were performed using the Mann–Whitney test for continuous variables and the Fisher's exact test for dichotomous variables. When comparing change over time within groups, the Wilcoxon signed rank test was used. All tests were two-tailed and were conducted at the 5% significance level.

3.4.3 Paper III

The statistical method used in Paper III was the Spearman's rank correlation coefficient test, non-parametric statistics.

3.4.4 Paper IV

165 men and women (psoriasis patients and controls) were randomly numbered by means of a Bernoulli process with a 50% probability. To test for significance between participants with and without psoriasis with regard to the different oral health-related clinical, radiographic and laboratory parameters, the two-sample t-test and the analysis of variance (ANOVA) for continuous variables were used. The Fisher's exact test and the Pearson's chi-square were used with regard to categorical variables. A logistic regression analysis was performed to confirm significant differences between the groups while checking for possible confounders.

4 RESULTS

4.1 Paper I

Staphylococcus aureus was found in 38% of the untreated group compared to 4% in the control group, p<0,005 (*Table 1*). *S. aureus* was found in 54% of the treated group but, compared to the untreated group, there was no statistically significant difference. *Streptococcus haemolyticus group G* was found in the untreated group only. Coagulase-negative staphylococci were the most common species in the control group (*Table 1*). The culture findings in the different intertriginous areas in the three groups are presented in *Table 2*. Cultures were taken mainly from the inguinal areas. *Candida* was not found in any of the intertriginous areas. One single case of *Trichophyton rubrum* was the only dermatophyte cultured, and it was found in the treated group.

Table 1. Culture findings in the three groups.1.Untreated group, n=32. 2.Treated group, n=13. 3 Control group, n=19 (*25 sampling sites*).

Culture findings	**Psoriasis**		**Controls**
	Untreated	Treated	
	% (n)	% (n)	% (n)
Staph. aureus	38 (12)	54 (7)	4 (1)
Coagulasneg. Staph.	59 (19)	46 (6)	92 (23)
Str. haemolyticus Gr. A	-	8 (1)	-
Str. haemolyticus Gr. B	13 (4)	15 (2)	-
Str. haemolyticus Gr. C	-	-	4 (1)
Str. haemolyticus Gr. G	19 (6)	-	-
Enterococcus	6 (2)	-	-
Diphteroids	13 (4)	-	28 (7)
Proteus	3 (1)	-	-
Gramneg. flora	16 (5)	8 (1)	-
Candida	-	-	-
Dermatophytes	-	8 (1)	-

Table 2. Culture findings from the intertriginous areas in the three groups (70 samples).

Culture findings	**Sampling sites**				
	Inguinal n=43 % (n)	Axillary n=4 % (n)	Submammary n=4 % (n)	Intergluteal n=16 % (n)	Umbilicus n=3 % (n)
Staph. aureus	28 (12)	25 (1)	25 (1)	25 (4)	67 (2)
Coagulasneg. Staph.	70 (30)	75 (3)	100 (4)	62 (10)	33 (1)
Str. haemolyticus Gr. A	2 (1)	-	-	-	-
Str. haemolyticus Gr. B	9 (4)	-	25 (1)	6 (1)	33 (1)
Str. haemolyticus Gr. C	-	-	-	6 (1)	-
Str. haemolyticus Gr. G	9 (4)	25 (1)	-	6 (1)	-
Enterococcus	5 (2)	-	-	-	-
Diphteroids	9 (4)	25 (1)	-	38 (6)	-
Proteus	2 (1)	-	-	-	-
Gramneg. flora	9 (4)	-	-	12 (2)	-
Candida	-	-	-	-	-
Dermatophytes	2 (1)	-	-	-	-

4.2 Paper II

Eighty-four patients were randomised. Sixteen patients were withdrawn from the study before the first dose of treatment. The reason for withdrawal in the methotrexate group was laboratory abnormalities (2 patients) and withdrawn consent (2 patients), and for the ciclosporin group, laboratory abnormalities (5 patients) and withdrawn consent (5 patients). Two patients were considered to be ineligible: one patient improving a great deal after a holiday in the sun and the other was withdrawn by the investigator due to previous frequent sun exposure. Thirty-seven patients in the methotrexate group and 31 patients in the ciclosporin group started treatment, and all were included in analysis at week 12.

Demographic data is presented in *Table 3*. The majority of the patients in both groups were males. There was no difference between the groups regarding medical history, previous psoriasis treatment, marital status, home district and educational level. There was six pensioners in the methotrexate group but none in the ciclosporin group (p=0.024). The patients were allowed to use topical treatment during the study since we wanted the study to reflect the clinical practice. *Table 4* shows that the use of topical steroids, calcipotriol and emollients was similar in both of the groups and, after 12

weeks of treatment with methotrexate or ciclosporin, the use of group III and IV steroids and calcipotriol was reduced.

Effectiveness. The PASI scores at baseline, week 4, week 8 and week 12, are presented in *Table 5*. Ciclosporin was found to be more effective than methotrexate at 4, 8 and 12 weeks of treatment (p=0.0161; p=0.0018; p=0.0028). The PASI change at 12 weeks was 58% in the methotrexate group and 72% in the ciclosporin group. PASI 75 was achieved by 24% of the patients in the methotrexate group and by 58% in the ciclosporin group (p = 0.0094). PASI 90 was achieved by 11% of the patients in the methotrexate group and by 29% in the ciclosporin group (n.s.). 65% of the patients in the methotrexate group and 87% in the ciclosporin group achieved PASI 50 (n.s.).

Quality of life. The mean DLQI scores at baseline, week 4, week 8 and week 12, are presented in *Table 5*. At 8 weeks of treatment, the mean change in the DLQI at 8 weeks was 42% in the methotrexate group and 71% in the ciclosporin group (p=0.0078) but no significant differences were found between the groups at 12 weeks.

The mean values of the subscales of the SF-36 in the different groups are shown in *Figure 2.* In the methotrexate group, there was a significant mean percentage change in improvement from baseline at 12 weeks in PF (p=0.0007), BP (p=0.0017) and RE (p=0.0156) and in the ciclosporin group in BP (p=0.0032) and MH (p=0.0197). A significant mean percentage change in improvement between the groups at 12 weeks was seen in PF, meaning that methotrexate led to a greater improvement than ciclosporin (p=0.0492).

Subjective measure of disease activity. The mean VAS scores at baseline in week 4, week 8 and week 12, are presented in *Table 5*. The mean change in the VAS was in the methotrexate and ciclosporin groups respectively: 37 % and 53% week 4 (p=0.0078), 46% and 69% week 8 (p=0.0336) and 58% and 70% week 12 (p=0.0014), showing a significantly greater improvement in the ciclosporin group compared to the methotrexate group.

Adverse events. Side-effects were reported by 78% of the patients in the methotrexate group and 97% in the ciclosporin group. All adverse events registered in the 12 weeks study, are presented in *Table 6*. Fatigue was reported by nearly half (48%) of the patients in the ciclosporin group and 16% in the methotrexate group (p=0.0076). Gastrointestinal complaints were common, particularly nausea, but no difference between the groups was seen. No differences were seen concerning infection, common cold being the most

common. Elevated liver enzymes were reported in the methotrexate group only ($p=0.0133$) and elevated creatinine in the ciclosporin group only ($p=0.0067$). Paresthesias was reported by 35% of the patients in the ciclosporin group compared to none in the methotrexate group ($p<0001$). Hypertension, myalgia, muscle cramp, hypertrichosis and gingiva hyperplasia occurred in the ciclosporin group only. No serious adverse events were recorded. Due to adverse effects, around one third of the patients in both of the treatment groups needed to have the dose lowered or failed to increase the dose. Four patients in the ciclosporin group discontinued treatment due mainly to fatigue and gastrointestinal symptoms. Four patients in the methotrexate group and one patient in the ciclosporin group had to discontinue treatment temporarily due to infections. Two patients in the methotrexate group and one in the ciclosporin group were given antibiotics. All of the patients in the methotrexate group continued treatment, but four patients in the ciclosporin group discontinued treatment mainly because of fatigue and gastrointestinal symptoms.

Table 3. Baseline characteristics of the psoriasis patients receiving methotrexate or ciclosporin in Paper II.

Characteristics	Methotrexate (N=37)	Ciclosporin (N=31)
Number of patients randomized	41	43
Number of patients included in analysis	37	31
Gender (M/F)	28/9	27/4
Age (years)(mean ± SD)	48±14	45±14
Weight (kg)(mean ± SD)	85±16	87±15
PASI (mean±SD)	14.1±7.0	15.5±6.3
DLQI (mean±SD	7.9±5.8	9.3±6.0
VAS (mean±SD	63.9±18.9	66.2 ±18.7
Medical history		
No. of patients receiving daily medication	17	7
Cardiovascular	7	2
Diabetes	1	0
Gastric	3	1
Psychiatric	5	2
Hypothyreosis	1	0
Musculoskeletal	4	1
Osteoporosis	0	1
Obesity	1	0
Urogenital	1	0
Allergic	1	0
Migraine	1	0
Chronic Obstructive Pulmonary Disease	0	1
Previous psoriasis treatment		
Topical only	3	6
UVB	33	25
PUVA	3	5
Acitretin	2	1
Methotrexate	2	1
Ciclosporin	0	2
Marital status		
Married/Partner	31	20
Single	4	4
Widowed/Divorced	2	7
Home district	(*N=36*)	
Rural area	16	11
Urban area <50 000	9	8
Urban area >50 000	11	12
Education level		(*N=30*)
Nine-year compulsory school	18	12
High school	15	10
University	4	8
Occupation	(*N=33*)	
Student	1	2
Employed	24	26
Unemployed	0	1
Pensioner	6	0
Other	2	2

Table 4. Use of topical treatment in the methotrexate and ciclosporin groups at Baseline and after 12 weeks of treatment.

Topical treatment	Methotrexate (N=37)		Ciclosporin (N=31)	
	Baseline	Week 12	Baseline	Week 12
Steroid group I	1	1	1	2
Steroid group II	1	2	4	4
Steroid group III	8	4	11	6
Steroid group IV	11	6	5	1
Calcipotriol	11	6	5	2
Emollients only	10	9	7	9
None	5	10	4	10

Table 5. The outcome measures of the PASI, the DLQI and the VAS at baseline, week 4 (except for the DLQI), week 8 and week 12.

Outcome measures (mean±SD)	Methotrexate (N=37)	Ciclosporin (N=31)
PASI baseline	14.1±7.0	15.5±6.3
PASI week 4	9.3±6.1	7.4±3.8
PASI week 8	7.2±4.8	4.6±3.3
PASI week 12	5.6±3.8	3.6±3.0
DLQI baseline	7.9±5.8	9.3±6.0
DLQI week 8	4.0±4.1	2.5±2.8
DLQI week 12	2.5±2.6	2.5±3.8
VAS baseline	63.9±18.9	66.2±18.7
VAS week 4	41.0±25.0	30.2±20.5
VAS week 8	34.2±21.3	19.5±20.6
VAS week 12	26.0±18.8	18.3±22.1

Figure 2. The mean values of the subscales of SF-36 in the methotrexate and ciclosporin groups, at baseline, week 8 and week 12. Physical functioning (PF), role-physical (RP), bodily pain (BP), general health (GH) vitality (VT), social functioning (SF), role-emotional (RE), mental health (MH).

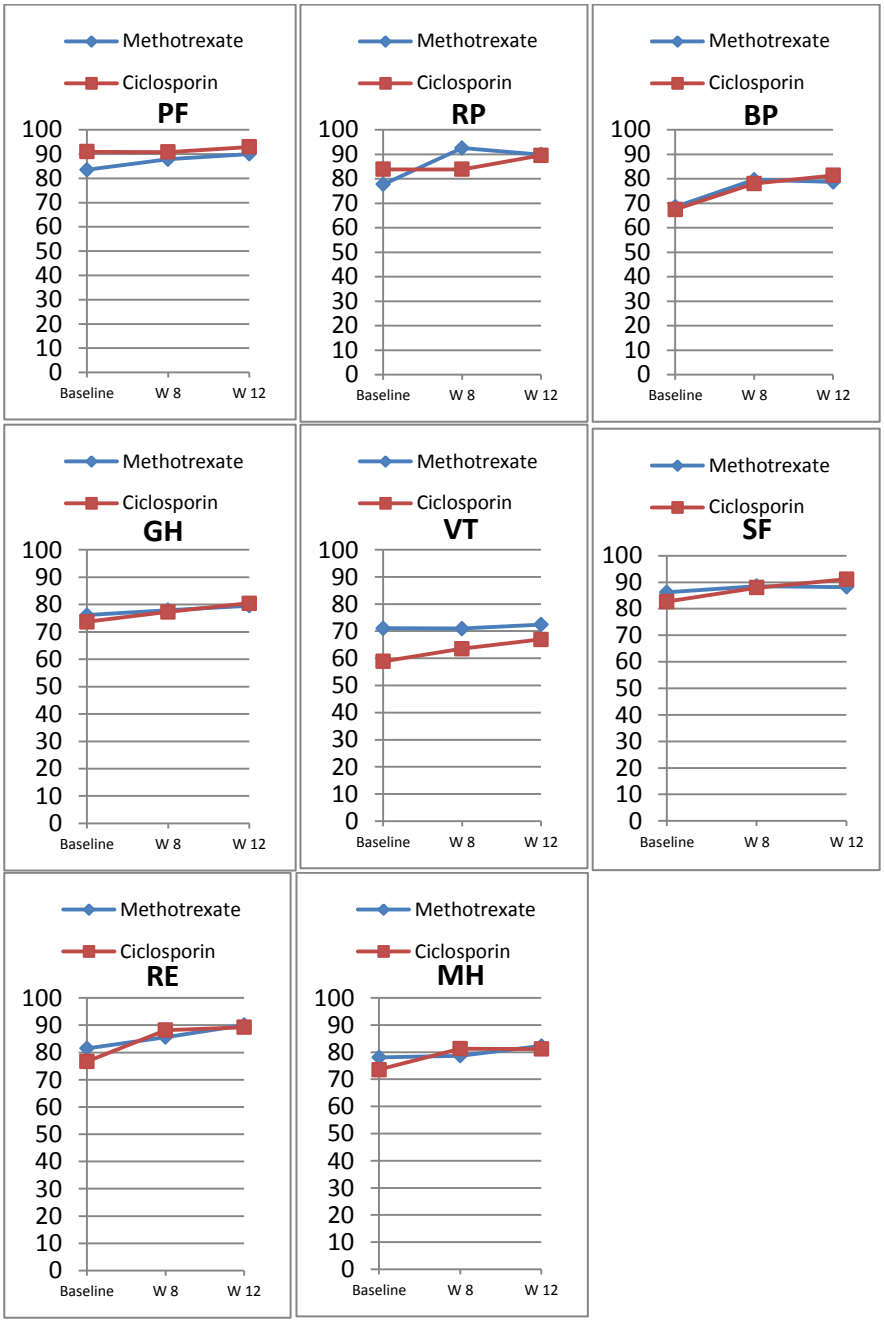


Table 6. All adverse events registered during 12 weeks of treatment with methotrexate or ciclosporin.

Adverse events	Methotrexate (N=37)	Ciclosporin (N=31)	p-value[a]
Fatigue	6	15	**
Headache	5	9	
Paresthesia	0	11	****
Hypertension	0	2	
Gastrointestinal			
Nausea	10	7	
Diarrhoea	2	4	
Flatulence	2	0	
Stomach ache	1	0	
Epigastralgia	1	2	
Emesis	0	1	
Infection			
Common Cold	7	7	
Urinary infection	1	0	
Extern otitis	1	0	
Bronchitis	2	1	
Gastroenteritis	2	3	
Tonsillitis	1	0	
Herpes	1	0	
Musculoskeletal			
Myalgia	0	5	*
Arthralgia	4	5	
Muscle cramp	0	4	*
Urinary tract (not infection)			
Dark urine	0	2	
Urgency	1	4	
Kidney pain	1	0	
Nephrolithiasis	0	1	
Laboratory abnormalities			
Elevated liver enzymes	7	0	*
Hyperlipidemia	0	1	
Electrolytes	0	1	
Elevated creatinine	0	6	**
Ciclosporin concentration	0	6	†
Miscellaneous AEs			
Weight gain	1	1	
Increased appetite	1	1	
Reduced appetite	1	1	
Nose bleed	2	0	
Gingiva hyperplasia	0	2	
Hypertrichosis	0	4	*
Hair loss	2	0	
Itch/burning skin	3	1	
Actinic keratosis	0	1	
Vertigo	1	1	

[a]Fischer's excact test
p<0.05 *, p<0.01 **, p<0.001 ***, p<0.0001****

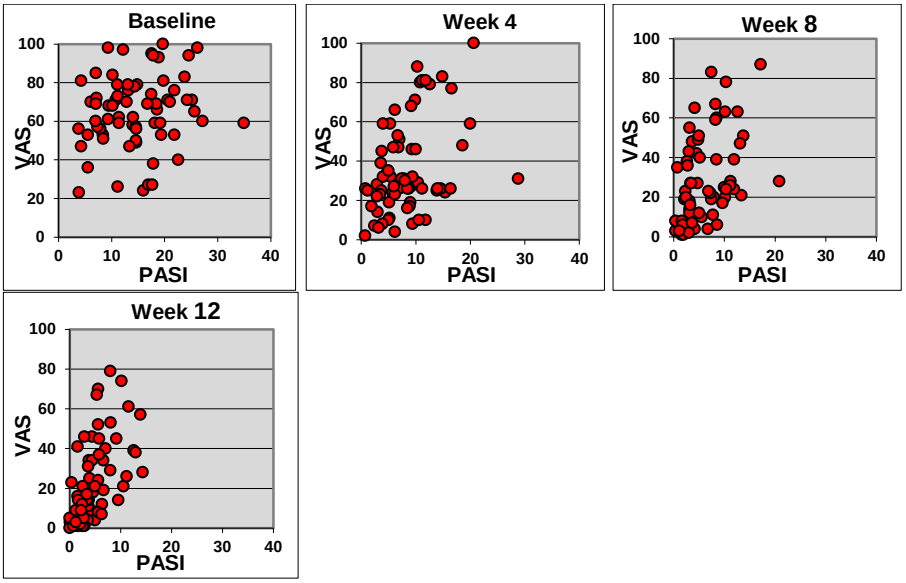
† not applicable

4.3 Paper III

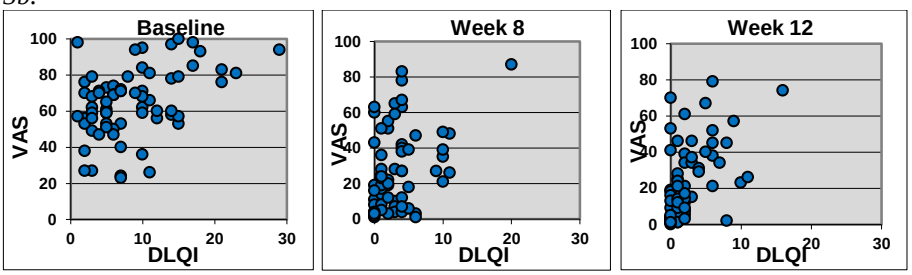
There was a significant but modest correlation between the VAS and the DLQI at each visit (*Figure 3b*) and also between the VAS and the PASI except at the baseline visit (*Figure 3a*). The PASI and the DLQI correlated only at week 12 (*Figure 3c*). Correlation, expressed as a percentage change from baseline to week 12, was found between the VAS and the PASI (**see Figure 2a, p.2, Paper III**) and between the VAS and the DLQI (**see Figure 2b, p.2, Paper III**) and also between the DLQI and the PASI (data not shown). Changes in disease activity measured by the VAS are demonstrated in *Figure 4.* At baseline none of the patients experienced VAS 0-20. 85% of the patients who was achieving a 75% improvement in the PASI at week 12, had a VAS score of 0-20. The majority of the patients who achieved a 75% improvement in the PASI also had low scores in the VAS and the DLQI (*Figure 5*).

Figure 3.Linear correlations at baseline, week 4, week 8 and week 12.
3a.Between the VAS and the PASI at baseline (r= 0.18, p=0.1310), w. 4(r= 0.40, p=0.0007), w. 8 (r= 0.57, p<0.0001) and w. 12 (r= 0.69, p<0.0001)
3b. Between the VAS and the DLQI at baseline (r = 0.39, p=0.0011), w. 8 (r= 0.31, p=0.0111) and w.12 (r= 0.55, p<0.0001)
3c.Between the PASI and the DLQI at baseline (r= 0.00, p=0.9829), w. 8 (r= 0.17, p=0.1715) and w.12 (r= 0.45, p=0.0001)

3a.



3b.



3c.

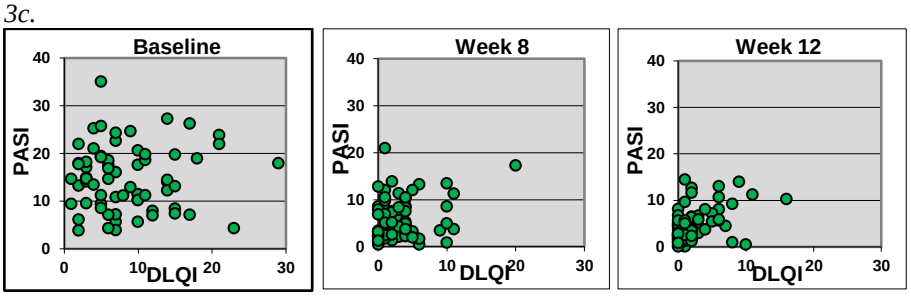


Figure 4. Percentage changes in disease activity (no complaints to worst complaints) measured by the VAS. Baseline values compared with different PASI response at week 12 (p=0.002).
Baseline, n=68; PASI<50, n=17; PASI 50, n=24; PASI 75, n=27

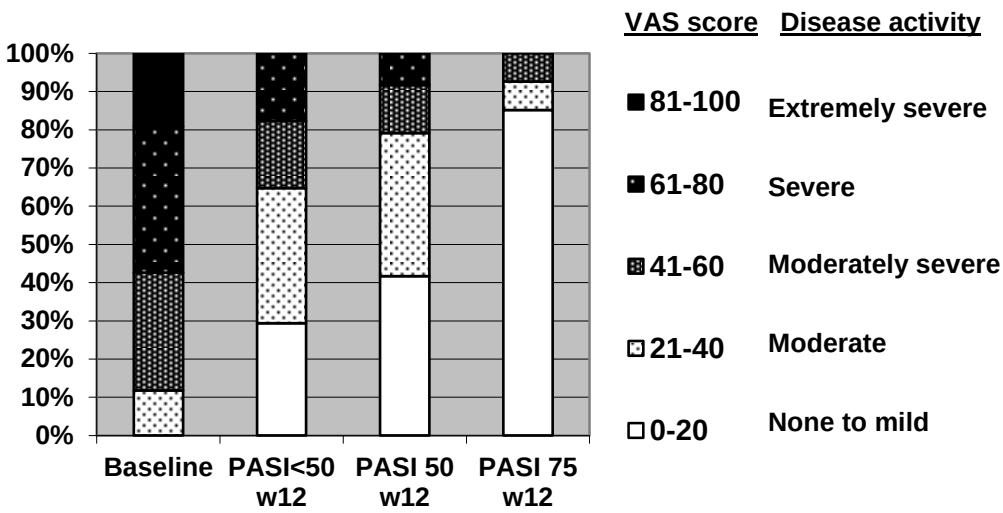
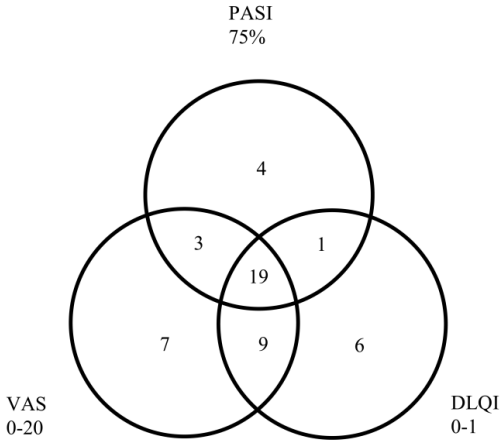


Figure 5. The number of all patients (49 out of 68) achieving at least 75 % improvement in the PASI, scoring 0-20 in the VAS or 0-1 in the DLQI, at week 12.



4.4 Paper IV

In Paper IV, a total of 165 patients and controls were randomised. One person in the control group withdrew from the study because she did not agree to undergo all parts of the examination. A total of 20 subjects, did not proceed to the odontology visit (11 in the psoriatic group and 9 in the control group) Most of the drop outs were due to poor coordination between the different departments, resulting in participants losing interest in completing the study and some had moved. One psoriasis patient did not attend the rheumatology clinic and was therefore not included in the analysis. A total of 143 patients were included in the analysis, 89 psoriasis patients and 54 controls. Characteristics of the psoriasis and the control group are shown in *Table 7.*

Cariological and periodontal findings. No significant differences in risk factors such as smoking, high sugar intake, poor oral hygiene or use of fluoride products were seen between the psoriasis group and controls (**see Table 2, p.24, Paper IV**). No differences were seen between the groups, with regard to the number of decayed or filled tooth surfaces. The psoriasis patients had a lower salivary buffer capacity and fewer remaining teeth than the control group ($p<0.05$). The psoriasis group also had a significantly lower radiographic alveolar bone level than controls, but only prior to checking for confounders (age, gender, BMI, smoking, diabetes, cardiovascular and other systemic diseases and medication). No significant differences were seen between the groups regarding the severity of periodontal disease. Severity is categorised as: healthy/gingivitis, previous periodontitis, mild periodontitis and moderate/severe periodontitis. 24% in the psoriasis group and 13% in the control group were in the moderate/severe category.

The prevalence of oral mucosal lesions in the psoriasis group was 48% and in the control group 44% (n.s.). No complaints or concerns were reported by any of the participants regarding the lesions observed when using the visual analogue scale. Thirty-nine percent of the total sample presented with tongue lesions, including fissured tongues (13%), hairy tongues (12%), geographic tongues (1%) and other tongue lesions (12%). Alveolar bony exostosis or palatal tori was present in 26% of the psoriasis group and 13% of the non-psoriasis group (n.s.).

More than half of the participants in both of the groups were taking regular medication for diseases other than psoriasis. These included non-steroidal

anti-inflammatory drugs (NSAID), acetylsalicylic acid, antidepressants and medication for hypertension, hyperlipidaemia, diabetes, gastritis and hypothyreosis. Antidepressants were more common in the control group compared to the psoriasis group (17% and 6% respectively, $p < 0.05$). However, when combining the patients' medication list with the patients' reports of ill health, there was no significant difference between the groups, regarding psychiatric morbidity. Musculoskeletal diseases were more common in the psoriasis group (p=0.041) (*Table 7*).

28% of the psoriasis patients had psoriatic arthritis. The clinical characteristics are presented in **Table 1, p.22, Paper IV**.

Overweight and obesity were seen more frequently in the psoriasis group compared to the control group (78% and 59% respectively, $p<0.05$) (*Table 7*). In the psoriasis group, significantly more men than women (89% and 65%, respectively, p=0.010) were overweight or obese, but no significant difference between the genders was seen in the control group (62% and 58% respectively, p=0.784). The levels of C-reactive protein were above normal (≥5mg/l) in 28% of the psoriasis patients (n=81) compared to 8% in the control group (n=48) $p<0.05$.

The mean age at psoriasis onset was 28 years. *Figure 6* shows the age of onset (males and females). Females had earlier onset than males (mean age 24 and 31 years respectively). There were a few correlations between the age at psoriasis onset and a number of clinical and radiographic parameters (while checking the BMI). The age of psoriasis onset was positively correlated with decayed, missing or filled tooth surfaces (DMFS) (p=0.004), number of bleedings on probing (BoP) sites (p=0.040), and the number of sites with probing pocket depth (PPD) ≥ 5 mm (p=0.007). It was negatively correlated with the number of sites with PPD ≤ 4 mm (p=0.031).

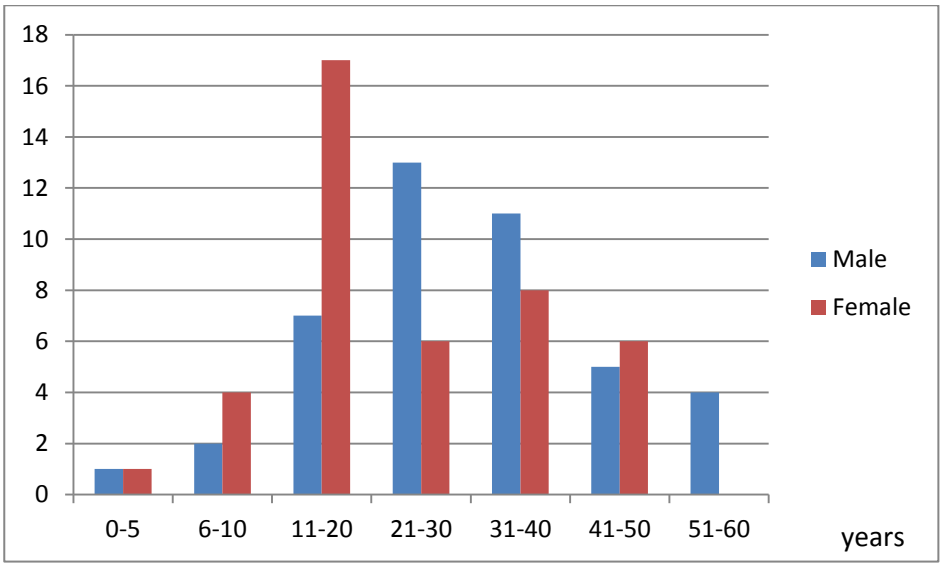
Table 7. Characteristics of the psoriasis patients and controls.

Characteristics	Psoriasis	Controls	p-value[a]
No. of patients randomised	101	64	
No. of patients included in analysis	89	54	
Gender (M/F)	46/43	21/33	
Age (years)(mean ± SD) (range)	59±10 (40-86)	60±11 (41-79)	
Age at psoriasis onset (years) (n=85)	28 ±14	-	
Weight (kg) (mean ± SD) (range)	83 ± 18 (49-131)	80 ±23 (51-198)	
BMI (kg/m^2) (mean± SD)	28 ± 5	27±7	
BMI ≥25 (% of the patients)	53	42	
BMI ≥30 (% of the patients)	25	17	
Psoriasis arthritis	28	-	
Concomitant diseases (self-reported ill health + medication (% of the patients)			
Hypertension	28	24	
Hyperlipidaemia	18	15	
Diabetes	10	2	
Gastrointestinal	10	20	
Psychiatric	13	17	
Hypothyreosis	9	5	
Musculoskeletal	37	20	*
Regular medication (% of the patients)	57	52	
Previous psoriasis treatment (% of the patients)			
UVB	90	-	
PUVA	14	-	
Grenz rays	12	-	
Acitretin	1	-	
Methotrexate	24	-	
Ciclosporin	2	-	
Biologics	5	-	
PASI (mean±SD) (range)	4.6±2.6 (1.0-18.1)	-	
BSA (mean±SD (range)	4.0±3.9 (0.5-28.0)	-	

[a]Fisher's exact test.

p<0.05 *

Figure 6. The age at psoriasis onset in the psoriasis group (n= 85).



5 DISCUSSION

5.1 Paper I

Intertriginous psoriasis lesions are characterised by moist lesions with bright red color, and are often believed to be colonised by microorganisms, mainly *Candida* and *S. aureus*, and treatment with topical steroids combined with antibiotics/antifungals is therefore routinely given. Since the evidence for using steroid combinations was poor, we wanted to find out more about the flora in intertriginous areas in psoriatic patients.

In our study, *S. aureus* was seen more frequently in both the treated and untreated psoriasis groups compared to the control group. This is in accordance with other studies on psoriasis but without cultures from intertriginous areas. (145; 146; 147) However, the important thing is whether there is an infection or colonisation. We favour colonisation in our study due to the fact that cultures were rarely monocultures.

Streptococcus haemolyticus Group G was found in 19 % in the untreated psoriasis group. It is well-known that β-haemolytic streptococci (Group A, C and G) isolated from the tonsils, are associated with both acute and chronic forms of psoriasis. (20; 21) A small number of case reports have shown induction of guttate psoriasis as a result of infection of perianal skin by Group A streptococci. (148) Smith et al. (149) investigated cases of intertrigo in different diseases and found that streptococci were present in all of the fissured or eroded lesions, and nine out of 15 strains were haemolytic. One shortcoming in our study is that we did not make any clinical assessments of the intertriginous areas. However, patients with a positive β-haemolytic streptococcus culture should be treated even in the absence of infection clinically because of the risk of the psoriasis trigger mechanism or the development of erysipelas. (150)

In our study, *Candida* was not found in any of the intertriginous areas. Leibovici et al. (151) made a prospective study where the prevalence of Candida on the tongue, axillae and groins of psoriatic patients was compared with atopic dermatitis patients and healthy controls. The result of their study did not reveal higher prevalence of Candida in the axillae and groins of either psoriatic or atopic dermatitis patients. Leung et al (22) reported cutaneous infection with *C. albicans* in association with the exacerbation of skin

lesions. The normal microbial flora acts as a natural antagonist against abundant fungal growth. Rebora (152) has made a comment on our negative finding of *Candida*, i.e. that it is not surprising that we failed to cultivate because *Candida* acts as a primer and has a köbnerizing effect and disappears when Gram-negative bacteria come along to replace it. (153) That could be true and there is no need for antifungal treatment in any case if there are no signs of the manifestation of a *Candida* infection. Even if *Candida* is seldom found among patients with intertriginous psoriasis, one has to be aware of clinical signs of the manifestation of a *Candida* infection, such as satellite pustules and oozing. Buslau et al (154) found an improvement in more than half of patients treated systemically with antifungals, which could support the role for *Candida* in exacerbation of psoriasis. The mechanism by which *Candida* may exacerbate psoriasis remains to be investigated. One possibility is that Candida produces superantigenic factors that stimulate T cell activation in a similar manner to streptococcal and staphylococcal toxins. (22)

Malassezia yeasts are normally part of the skin flora, but they are also associated with several common dermatologic conditions. Unfortunately, *Malassezia* cultures were not performed in our study. The role of the *Malassezia* species in psoriasis has yet to be determined, but several reports indicate a role played by the *Malassezia* yeasts in psoriasis, especially psoriasis involving the scalp, eyebrows, ears and seborrhoeic areas of the trunk. It has also been shown that the antifungal agent ketoconazole may potentially affect psoriasis through its antifungal action against *Malassezia* or indirectly by suppressing *Malassezia* induced lymphocyte-mediated immune responses. (24; 155; 156; 157)

The question is whether to use topical steroids along with a combination of antibiotics and antifungals, or not to use them at all. It has been proposed that a steroid-antibiotic combination would be justified because the dermatologist cannot undertake a bacteriological analysis of every case, and he must endeavour to achieve a safety factor through broad coverage. (158) However, by reducing the exudate, the topical steroids alone can aid the restoration of the normal microflora and make the affected areas less suitable for bacterial pathogens. This is one reason why corticosteroids used on their own can be beneficial in infected dermatoses. There is no evidence to show that corticosteroids potentiate topical infections. (158) There also are some disadvantages of topical antibacterial agents with a risk of the emergence of

resistant pathogens, suppression of the normal skin flora, contact sensitisation and skin staining. (159)

It is not always possible to know whether there is an infection that needs to be treated with antibiotics or with antifungals. In general, we recommend that intertriginous psoriasis be treated with topical steroids alone and the routine use of antibacterial combinations be avoided. When fissures or erosions are present, we suggest taking samples for bacterial cultures and, when pathogens such as streptococcus haemolyticus are found, oral antibiotics should be given. When redness and satellite pustules are found and the patient's fungal culture is positive, treatment with antimycotic agents is needed. (151)
However, in clinical practice, azoles combined with topical steroids are often used and appear to be helpful in the treatment of some patients with intertriginous psoriasis. There may also be an overlap of flexural psoriasis with seborrheic dermatitis. (160) Van Cutsem et al. (161) suggest that ketoconazole has an anti-inflammatory effect, which may explain some of its beneficial effects irrespective of any *Candida* infection. Topical imidazoles also have some broad-spectrum antibacterial activity along with the well-known activity against fungi and yeast. (162) A combination of topical steroids and imidazoles could therefore be beneficial in the treatment of intertriginous psoriasis.

5.2 Paper II

The initial ideas to carry out our study originated from an article published in 1997. It was a review of studies concerning treatments for severe psoriasis. (163) In that meta-analysis, a total of 665 studies of treatment with UVB, PUVA, methotrexate, retinoids and ciclosporin, were analysed, but only 129 studies were of satisfactory quality to be included in the analysis. It was not possible to include any study of methotrexate. We therefore wanted to conduct a randomised controlled trial (RCT) comparing methotrexate and ciclosporin using the most common assessment tools in a manner that reflected clinical practice and with no involvement from the pharmaceutical companies. At that time, no biological therapies for psoriasis were available on the market. During the inclusion period of our study, two studies

comparing methotrexate and ciclosporin, were published: Heydendael et al. (2003) (164) and Sandhu et al. (2003) (165) (*Table 8*).

The primary outcome measure was the PASI. We found ciclosporin to be more effective than methotrexate at twelve weeks of treatment, with a mean PASI change of 58% in the methotrexate group and 72% in the ciclosporin group. In the studies by Heydendael et al. (164) and Sandhu et al. (165), no statistically significant difference in the PASI was found between the groups. In the study by Heydendael et al. (164), the mean PASI change at 16 weeks, was 64% in the methotrexate group and 72% in the ciclosporin group. In the study by Sandhu et al. (165), the mean PASI change at 12 weeks was 98% in the methotrexate group and 85% in the ciclosporin group. Unfortunately, the study by Sandhu et al. (165) was of limited value due to very small size and a heterogeneous patient population. In our study, PASI 75 was achieved by 24% of the patients in the methotrexate group and by 58% in the ciclosporin group. In the study by Heydendael et al. (164). PASI 75 was achieved in 60 % in the methotrexate group and 71 % in the ciclosporin group. In the small study by Sandhu et al. (165), PASI 75 was achieved in all patients but one, in the ciclosporin group. Since our study was published, three other studies comparing methotrexate with biologics have been published (166; 167; 168) (*Table 8*). In these studies, PASI 75 was achieved by between 36 % and 42% of the methotrexate patients. Despite the fact that it is hazardous to make comparisons between different studies, there are some matters that are up for discussion. Our finding of only 24 % of the methotrexate patients achieving PASI 75 is noteworthy. However, in the three latter studies, a maximum methotrexate dose of 20-25 mg/week was administered. In our study, the maximum dose of methotrexate was 15 mg/week, but 54% of the patients did not receive that maximum dose. The low doses in our study might therefore constitute a plausible explanation for our result in the methotrexate group. However, of the ten patients in the methotrexate group achieving a $\geq$ 75 % improvement in the PASI, only 2 patients had a methotrexate dose of 15mg/week. The other patients had doses of 12.5 mg/week (1 patient), 10 mg/week (5 patients), and 7.5 mg/week (2 patients). Another explanation for our result could be the short length of the study. All studies except for the study by Sandhu et al. (165) had the evaluation point between 16 and 24 weeks. The study of Sandhu et al. (165) had very high methotrexate doses, however. The recommendation in clinical practice today in Sweden is a maximum methotrexate dose of 20mg/week (169).

To use or not to use supplementary folic acid in the treatment with methotrexate has been debated. In our study, supplementary folic acid was administered. This was in accordance with earlier findings showing a lower risk of gastrointestinal side effects and elevated liver enzyme levels. (87; 170) Supplementary folic acid is not generally believed to compromise the effectiveness of methotrexate (85), although in two randomised controlled psoriasis studies, it was demonstrated that folate supplementation reduced clinical efficacy but improved tolerability. (171; 172) In the other studies presented in *Table 8* (166; 167; 168) either no folate supplementation or a folate supplementation of 5 mg per week was administered. Our more frequent use of folate may thus have contributed to our result.

In four randomised placebo controlled trials, ciclosporin was shown to be effective in inducing remission in the doses between 2.5 and 5.0 mg/kg per day. (173; 174; 175; 176) In the study by Ellis et al. (173), 85 patients with severe psoriasis were given ciclosporin 3mg/kg per day or 5 mg/kg per day or 7.5 mg/kg per day or a placebo. After 8 weeks of treatment, 36 % in the first group, 65 % in the second group and 80 % in the third group were healed or almost healed (global score=score ranging from 1-7 concerning scaling erythema, plaque thickness and overall severity) but none in the placebo group. In a very small study by Van Joost (176), 10 patients were given ciclosporin 5.5 mg/kg per day for 4 weeks (thereafter in an open phase) and 10 patients were given a placebo. After 4 weeks of treatment, the mean PASI improvement in the ciclosporin group was 72% compared with 3% in the placebo group. PASI 75 in the ciclosporin group was 83%. In a study by Meffert et al. (175), 133 patients with moderate to severe plaque psoriasis were given ciclosporin 1.25 mg/kg per day or 2.5 mg/kg per day or a placebo. After ten weeks of treatment, the mean PASI change was 27 % in the first group, 51 % in the second group and 6 % in the placebo group. These studies show that higher doses of ciclosporin lead to a greater improvement. In our study, the proposed initial dose of ciclosporin was 3 mg/kg per day and that was concordant with the studies by Heydendael et al. (164) and Sandhu et al. (165) In our study, it was possible to increase the doses to a maximum dose of 5 mg/kg per day (also proposed in the study of Heydendael et al. (164) The actual doses at the start of treatment in our study, were in the range of 2.6-3.3 mg/kg per day and at 12 weeks of treatment, nine patients were given lower doses of between 2.0 – 2.5 mg/kg and only two patients were given

higher doses of between 3.4 and 4.4 mg/kg per day. The low doses were a result of side-effects.

Side-effects were reported more frequently in the ciclosporin group compared with the methotrexate group (97% and 78% respectively), and this is consistent with the study by Heydendael et al. (164) (83% and 67% respectively). Gastrointestinal symptoms were common side-effects in both the methotrexate and the ciclosporin groups, and we found no significant difference between the groups (35% and 39% respectively). Nausea was reported in 27 % of the patients in the methotrexate group and 22 % in the ciclosporin group, compared with 44 % and 9 % respectively in the study by Heydendael et al. (164) Lack of folate supplementation in the latter study is the most plausible explanation for the differences in the methotrexate groups. In the other studies mentioned (166; 167; 168) (*Table 8*), nausea was reported in 7 %, 8% and 12% respectively in the methotrexate groups. In our study, elevation of liver enzymes was usually mild and no patient in the methotrexate group had to discontinue treatment, contrary to the findings in the study by Heydendael et al. (164), where twelve patients (28 %) had to discontinue methotrexate treatment purely because of elevations of liver enzymes. The use of supplementary folic acid in our study and the fact that the methotrexate doses was lowered, may have contributed to the fact that all patients in the methotrexate group continued in the study. Four patients in the ciclosporin group discontinued treatment due mainly to fatigue and gastrointestinal symptoms. In the study by Heydendael et al. (164), only one patient in the ciclosporin group discontinued treatment because of adverse effects (elevation in bilirubin). In the study by Ellis et al. (173), patients who were given ciclosporin 3 mg/kg per day experienced fatigue (8%), gastrointestinal symptoms (28%), gingiva hyperplasia (8%), headache (16%), hypertrichosis (12%) and paraesthesia (16%). In our study, 48% of the patients reported fatigue, 39% gastrointestinal symptoms, 6% gingiva hyperplasia, 29% headache, 13 % hypertrichosis and 35% paraesthesisa. These figures may be a result of our study being 12 weeks, compared to 8 weeks in the study by Ellis et al. (173)

The second outcome measure in our study was quality of life, measured by the DLQI and the SF-36. The DLQI was not used in either of the other studies, comparing methotrexate and ciclosporin. (164; 165) The mean DLQI at week 12 showed no difference between the groups. (*Table 4*). However, a common estimate of the minimal clinically important difference of the DLQI

total score is a 5 point improvement. (42). From this perspective, it was found that 71% (22/31) of the ciclosporin patients had a ≥ 5-point DLQI reduction from baseline at week 12 compared with 38% (14/37) of the methotrexate patients, showing a significant improvement in quality of life in the ciclosporin group compared to methotrexate group (p=0.008). However, the result may have been influenced by a slightly higher mean score in the ciclosporin group at baseline. In the study by Barker et al. (167), 67% of the methotrexate patients had a ≥ 5-point DLQI reduction from baseline, but the mean score at baseline was remarkable higher than in our study (13.8 and 7.9 respectively. Another definition of a clinical meaningful response includes patients who achieve a DLQI score of 0-1, meaning the patients have no impairment on quality of life. (41; 45; 44) In week 12, 64% (20/31) of the ciclosporin patients compared to 40 % (15/37) of the methotrexate patients had a DLQI score of 0 or 1 (p=0.0563). In the study by Barker el al. (167), DLQI scores of 0 or 1 were found in 37% of the patients in week 16. Reich et al. (168) showed that 34 % of the patients in the methotrexate group had low DLQI scores of 0-1 in week 24. These figures are consistent with the finding in our study. The mean values of the subscales of the SF-36 in the different groups are shown in *Figure 2*. A significant mean percentage change in improvement between the groups at 12 weeks, was seen in the subscale physical functioning (PF), meaning the methotrexate group showed more improvement than the ciclosporin group (p = 0.0492). Heydendael et al. (164) found no significant differences in any of the subscales of the SF-36.The PF consists of questions concerning activities likely to be performed during an ordinary day, such as walking, running, lifting and carrying. At baseline, there was a slight although not statistically significant difference between the groups showing a lower PF in the methotrexate group. This might have contributed to the result. Another possible explanation is that the side-effects, such as myalgia, in the ciclosporin group, could lead to less improvement in terms of physical function.

Subjective measure of disease activity. The mean VAS change from baseline acquired statistical significance between the groups at 4, 8 and 12 weeks showing better improvement in the VAS score in the ciclosporin group than in the methotrexate group. No comparable studies have been found.

The strength of this multicentre RCT was that we conducted a study focusing on established psoriasis treatments, and with no involvement from the

pharmaceutical companies. The study reflected clinical practice in Sweden. This means that there could also be a shortcoming with our study because we allowed the patients to use topical treatment during the study, and this could lead to problems when comparing it with other studies. In our study, there was a large patient drop out following the randomisation due to laboratory abnormalities. In retrospect, we should have taken the laboratory tests before randomisation. On the other hand, we wanted to take only the necessary tests for each treatment regime and thus reflect clinical practice. Several outcome measures were used, and this study was the first comparative study of methotrexate and ciclosporin using the DLQI and the VAS. Methotrexate is without doubt the first-line therapy when systemic therapy is indicated. However, both methotrexate and ciclosporin treatments have their limitations due to long-term side-effects. A limitation of the study is the short treatment period. Since this study was carried out, new guidelines concerning folate supplementation have been issued, restricting folate supplementation to once a week. New treatment options for moderate to severe psoriasis have developed in recent years, and biologics therefore now constitute an alternative when traditional systemic treatments as methotrexate, ciclosporin, acitretin or PUVA fail. Due to the nephrotoxicity of ciclosporin, the use is limited, but it still plays a role as a short-term treatment and when rapid effect is needed. Since methotrexate is the most commonly-used treatment for moderate to severe psoriasis, there is a need for long-term studies concerning effectiveness, quality of life and safety.

Table 8. Presentation of six randomised controlled trials: three comparing methotrexate and ciclosporin: Flytström, Heydendael (164), Sandhu (165) and three comparing methotrexate with biologics: Saurat(166), Barker(167), Reich (168.)

	Flytström 2008	Heydendael[164] 2003	Sandhu[165] 2003	Saurat[166] 2008	Barker[167] 2011	Reich[168] 2011
Study design	Methotrexate/ Ciclosporin	Methotrexate/ Ciclosporin	Methotrexate/ Ciclosporin	Methotrexate/ Adalimumab/ Placebo	Methotrexate/ Infliximab	Methotrexate/ Briakinumab*
No. of patients	37 / 31	44 / 44	15 / 15	110 / 108 / 53	215 / 653	163/154
End points	12 weeks	16 weeks	12 weeks	16 weeks	16 weeks (*and 26 weeks*)	24 weeks (*and 52 weeks*)
Methotrexate doses	7,5 mg/w (when needed 15 mg/w)	15 mg/w	0,5 mg/kg/w (mean dose 27/mg/w)	7,5 mg/w (when needed increase to 25 mg/w)	15 mg weekly with a dose increase to 20 mg weekly at week 6	Start dose 5 mg/w, 10 mg/w, then 15 mg/w 2-9. Max dose 20mg w 10 and 25 w 16
Ciclosporin doses	3 mg/kg/day (when needed 5 mg/kg/day)	3 mg/kg/day (when needed 5 mg/kg/day)	3 mg/kg/day	-	-	-
Folate supple-mentation	5 mg daily except for methotrexate day	None	None	5 mg weekly, 48 h after methotrexate dose	Recommen-ded but not mandated	5 mg weekly
PASI 75	24%; 58%	60%; 71%	100%; 93%	36%; 80%; 19%	42%; 78%	40%; 82%

* Anti-interleukin-12/23 monoclonal antibody (not on the market)

5.3 Paper III

The VAS instrument was found to be a useful instrument reflecting both the patient´s assessment of the psoriasis severity and the impact on quality of life. We found a modest but significant relationship between the VAS and the DLQI and between the VAS and the PASI, which increased in magnitude over time. However, the VAS did not correlate with the PASI at baseline. One plausible explanation is that some patients with low baseline PASI scores experienced a major impact on quality of life. There also was a poor correlation between the PASI and the DLQI at baseline.

The main advantage of using the VAS compared to the PASI and the DLQI is that it saves time. It takes only a few seconds to obtain a score and imposes no inconvenience. (177) However, one negative aspect might be the need for abstract thinking, which can make it difficult to understand and complete for some patient groups. (178) The VAS and statistics have been heavily criticised. The VAS values are often treated as continuous quantitative data, but non-parametric studies show that clinical VAS values are not linear but represent only a regime and not absolute size and distance. (179; 180) In our study, non-parametric statistics were used.

The VAS has previously been used in different psoriasis studies, mainly to rate the intensity of itching. (51; 52; 54) In a prospective psoriasis survey (54), the relevance of standard assessment tools in clinical practice was investigated with the regard to treatment choice. The PASI and the BSA were used and also the VAS, representing the patient's self-assessment of the severity of psoriasis and the impact on quality of life (on a scale of 0-10). The instruments were not compared with one another, however.

In everyday clinical practice it is important for medical professionals to gain insight into the way in which psoriasis affects patients' lives. Psoriasis does not need to be extensive in order to impair quality of life. A visual analogue scale used in routine care could be a simple and excellent tool for both patient and clinician when discussing treatment options. Although further studies are needed to examine test-retest reliability and validity of the VAS in psoriasis assessment, we suggest that the VAS should be used as a complement to the PASI and DLQI or as a single tool for all psoriasis patients in everyday clinical practice.

5.4 Paper IV

In recent years, it has been shown that psoriasis is a disease, which in addition to psoriatic arthritis, is associated with several other major diseases such as gastrointestinal and liver diseases, cardiovascular disease, malignancy and psychiatric disease. At the Odontology Department in Gothenburg, dentists had noticed poor oral health among psoriasis patients, and suspected a possible correlation between the diseases. This was the reason why the dentists contacted us and the study was conducted.

No difference between the groups was seen regarding experience and risk of dental caries. The psoriasis group had a significantly lower salivary pH than the controls. The psoriatic patients with psoriatic arthritis had lower stimulated salivary secretion rates, and this was concordant with earlier findings. (181) The salivary function is important in the defence against caries. (182) Consequently, the dentist should consider the reduced salivary function as a possible caries risk indicator when dealing with patients with psoriasis, especially those with psoriasis arthritis. In literature, oral psoriasis lesions have been described as affecting the buccal mucosa, lip, palate and gingiva. There also appears to be an increase in the frequency of geographic tongue and fissured tongue in patients with psoriasis. (141; 142; 143) However, in our study, the prevalence of oral mucosal lesions or *Candida* showed no significant difference between the groups.

There was no difference between the group regarding experience and risk of periodontal disease. The psoriasis group had more missing teeth and lower radiographic alveolar bone levels compared to the controls. This finding was consistent with a recent study by Preus et al. (183) However, when we had checked for confounding factors in our study, there was no significant difference between the groups regarding alveolar bone level. In the case-control study by Preus et al (183), no checks for confounding factors took place.

The psoriasis group included significantly more overweight and obese people than the control group. This was concordant with several studies, demonstrating that patients with psoriasis are more frequently overweight. (13; 15; 114) The severity of psoriasis may also be linked to obesity. (13; 184; 185) although controversy still exists as to whether obesity is a result of psoriasis or a causative factor. (186) In a review by Suvan et al. (187), an association was found between being overweight or obese and having

periodontitis. The magnitude of the association is still unclear, however. Possible mechanisms behind the association might be a dysregulation of immune responses, with elevation of levels of acute phase proteins, pro-inflammatory cytokines and leukocyte counts in obesity as a result of adipose tissue endocrine activity. (188) In the laboratory analyses, significantly more patients in the psoriasis group had above normal CRP levels (≥ 5 mg/l), but no difference was seen in leukocyte counts. Since periodontitis is a chronic inflammatory and infectious disease, CRP levels have been of interest in patients with periodontitis. (189) Concentrations of TNF-a have been reported to be higher in periodontitis patients than periodontal healthy patients and have been shown to have been reduced following periodontal therapy. (190) Each of the chronic diseases of psoriasis, periodontitis and obesity is also independently associated with other factors such as smoking and insulin sensitivity. (188)

Within the limits of this study, we found no differences in dental caries or periodontal disease between the psoriasis patients and controls. The psoriasis patients had a lower salivary pH, and psoriatics with psoriatic arthritis had lower stimulated salivary secretion. These findings may predict a possible future risk of caries. In our study, most of the patients had low PASI and BSA scores, showing a mild psoriasis. Whether higher risk of caries or periodontal disease may be seen in a psoriasis group with more severe and untreated disease remains open for investigation. However, when looking at previous psoriasis treatments in the psoriasis group (*Table 7*), about 25% of the patients in our study could be considered to be in the category of moderate to severe disease.

6 CONCLUSION

We recommend that intertriginous psoriasis be treated with topical steroids alone and the routine use of antibacterial combinations be avoided. When fissures or erosions are present, we suggest taking samples for bacterial cultures, and when pathogens such as streptococcus haemolyticus are found, oral antibiotics should be administered.

We found ciclosporin to be more effective than methotrexate at twelve weeks of treatment. Due to the nephrotoxicity of ciclosporin, the long-term treatment value is limited, but it still plays a role in short-term treatment when a rapid effect is needed.

The VAS could be used as a complement to the PASI and the DLQI or as a single tool for psoriasis assessment in clinical practice.

No difference was seen between the psoriasis patients and controls regarding experience and risk of dental caries and periodontal disease. However, the psoriasis patients had a lower salivary pH and psoriatic patients with psoriatic arthritis had lower stimulated salivary secretion. These findings may predict a possible future risk of caries.

7 FUTURE PERSPECTIVES

Steroids combined with antifungals are frequently used for intertriginous psoriasis. Larger studies that pay particular attention to intertriginous areas are still lacking. It would therefore be interesting to conduct a randomised controlled trial concerning topical treatment with steroids compared to steroids combined with azoles, and with focus on bacteria and fungi, including *Malassezia*.

Methotrexate is the first-line treatment when systemic treatment is needed. However, there is sometimes a decline in the effect during the treatment period. Topical treatment or UV treatments are sometimes added. More studies in clinical practice are needed, with focus on optimising the methotrexate treatment by combining different treatments.

The VAS is a simple method to be used in a busy clinical setting. Further studies are needed to examine test-retest reliability and validity in the use in psoriatic patients.

More studies are needed, to investigate oral health in psoriasis patients. It would be interesting to conduct a study with focus on the early and late onset of psoriasis regarding dental caries and periodontal disease.

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