Psoriasis: Comorbidity and Treatment

Marlies Wakkee

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Psoriasis: Comorbidity and Treatment

Psoriasis: comorbiditeit en behandeling

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Promotor: Prof.dr. H.A.M. Neumann

Overige leden: Dr. J.M. Gelfand
Prof.dr. A. Hofman
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Copromotoren: Dr. R.M.C. Herings
Dr. T.E.C. Nijsten

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Chapter 1

Psoriasis, an introduction

M. Wakkee
T. Nijsten

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1.1 Epidemiology

Psoriasis is universal in occurrence, although the worldwide prevalence varies between 0.6% and 4.8%.[1] The prevalence of psoriasis in people of Caucasian descend is approximately 2%.[2] In the Netherlands it is therefore estimated that approximately 300,000 people are diagnosed as having psoriasis. Its prevalence is equal in men and women and can first appear at any age, from infancy to elderly, although the mean age of development has suggested to be around 30 years old.[3] Some studies suggest the presence of two forms of psoriasis related to the age at onset. Early onset psoriasis, which comprises approximately 75% of the psoriasis population, presents itself before the age of 40 mostly with a positive family history and with more severe disease. While late onset psoriasis presents itself after the age of 40 and may have a less severe clinical course.[4] However, other studies were not able to confirm the presence of more severe psoriasis in those subjects with an early age of onset.[5] The extent of body surface area affected by psoriasis is variable, but in most people the severity of their psoriasis is reasonably stable over time.[5] Based on a patient survey the prevalence of moderate to severe psoriasis (i.e. more than 3% of the body surface area affected) was recently estimated to be approximately 17%.[6]

Costs

For all chronic health conditions, the affected persons have greater health needs at any age making their costs disproportionately high.[7] It has been estimated that about half of all Americans has at least one chronic condition, which has replaced infectious and acute diseases as the dominant healthcare challenge in the last half century.[7] Also psoriasis poses a significant economic burden to society. Because of its chronic course, patients receiving a diagnosis of psoriasis early in life usually need lifelong care implying lifelong expenses. The increased application of systemic drugs has resulted in a decline in the number of hospitalizations due to psoriasis.[8] Nevertheless according to an Italian study dating from 2001 hospitalization for psoriasis still accounted for four-fifths of the costs, while therapies accounted for about one-eighth (systemic therapies were the most expensive) and office visits and day hospitals for the remainder. Perhaps somewhat different than in Italy, the hospitalization rate for psoriasis is rapidly declining in other European countries and US. For example, US dermatology departments often no longer have any hospital beds. With the growing therapeutic arsenal of anti-psoriatic drugs including biological therapies it would be of interest to investigate whether an increased proportion of resources is shifted from hospitalization towards prescription drugs as is observed for rheumatoid arthritis and inflammatory bowel disease.

In addition to direct medical costs, lost work time and reduced productivity also lead to indirect costs. Patients with severe disease from the U.K. reported an average lost of more than 25 days from work of the preceding year.[9] American patients missed an average of 2.3 days a year

because of the disease.[10] A part of the healthcare budget is also spent on treating comorbidities associated with psoriasis. Increasing awareness of these possible associations may affect these costs as well. In the U.S. more than half of the direct and indirect costs were estimated to be associated with treating these comorbidities.[11]

1.2 PATHOGENESIS

The exact pathogenesis of psoriasis remains unclear. Both keratinocytes and T cells are suggested to have key functions in its pathogenesis (Figure 1). Keratinocytes contribute to the cutaneous immune responses through the expression of cytokines and have shown an augmented expression of interleukin-23 (IL-23).[12] IL-23 is important to activate memory T cells to produce IFN-gamma (IFN-γ) which contributes to the perpetuation of the inflammatory process.[12]

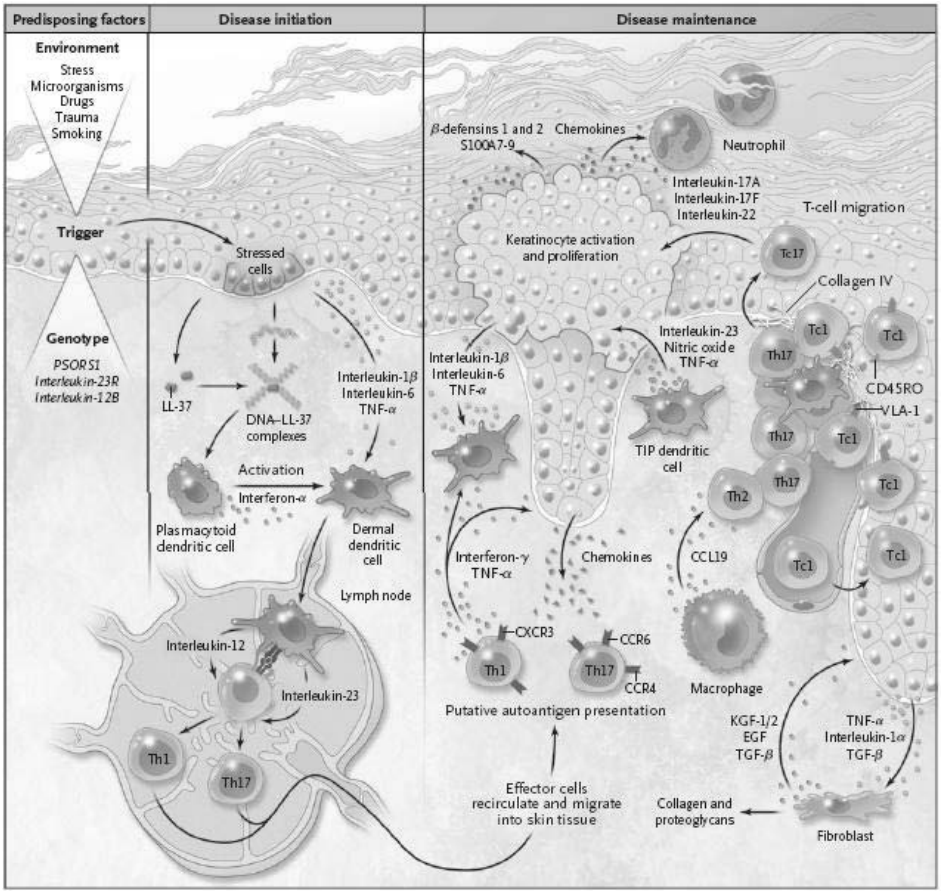

Figure 1. Proposed Schema of the Evolution of a Psoriatic Lesion from Initiation to Maintenance of Disease.[21]

Immunophenotyping has also confirmed the presence of T cell subsets in an early phase of the disease and together with the response of psoriasis to the T cell inhibiting therapy cyclosporine or a lymphocyte-selective toxin, T cells are suggested as the driving force in the pathogenesis of psoriasis.[13-15] At the site of inflammation, activated T-lymphocytes predominantly release type 1 cytokines like IFN-γ, tumor necrosis factor-α (TNF-α) and IL-2.[16] IFN-γ may contribute to hyperproliferation of keratinocytes in the skin by inhibiting their apoptosis. IL-2 stimulates the T-lymphocyte proliferation and TNF-α activates and increases keratinocyte proliferation. Other effects of TNF-α are stimulation of production of cytokines from T-lymphocytes and macrophages, chemokine release from macrophages, and the expression of adhesion molecules on vascular endothelial cells. The inflammation leads to oxidative stress that may have systemic consequences since high levels of oxidants stimulate the formation of atherosclerotic lesions in the vessel walls which may lead to a higher cardiovascular disease risk.

There are both external and systemic triggering factors that can elicit psoriasis. The elicitation of psoriasis by injury to the skin, which is also called the Koebner phenomenon is observed in approximately 25% of patients with psoriasis.[17] Infections may also induce or exacerbate psoriasis.[18] Strongest evidence exists for the induction of guttate psoriasis by a preceding tonsillar Streptococcus pyogenes infection, which appears to involve initial superantigenic T cell activation by streptococcal toxins, followed by an antigen-specific T cell response which could than also respond against auto-antigens of the skin.[19, 20] However, researchers have not been able to identify this superantigen.

Genetic factors

The risk that a child will develop psoriasis is about 40% if both parents are affected, 15% if one parent is affected and 5% if a sibling is affected by psoriasis.[22] Twin studies demonstrated that about 60% of monozygotic and 20% of dizygotic twins were concordant for psoriasis.[23] The major genetic determinant of psoriasis is the PSORS1 (PSORiasis Susceptibility 1) locus at chromosome 6p which probably accounts for 35% to 50% of the heritability of the disease.[24] Three genes have been the focus of research within this region. HLA-C (associated variant, HLA-Cw*0602-allel) encodes a class I MHD protein. CCHCR1 (associated variant, WWCC) encodes the x-helical rod protein 1 and corneodesmosin (associated variant, allel 5) encodes the protein corneodesmosin.[21] Other interesting associations outside of the PSORS1 locus are the deletion of the late cornified envelope 3B en 3C, which encode proteins that have a role in the skin barrier function[25] and the higher genomic copy number of beta-defensins that have both antimicrobial and proinflammatory properties.[26]

1.3 Clinical features

Chronic plaque psoriasis (psoriasis vulgaris), the most common variant of psoriasis, accounts for approximately 90% of all cases.[27] It is characterized by erythematous, infiltrated hyperkeratotic lesions that are sharply demarcated. Psoriasis vulgaris skin plaques are often symmetrical and primarily involve the elbows, knees, scalp and buttocks and sites of local trauma (Koebner's phenomenon). Other distinct characteristics are the noncoherent, silvery scales, the Auspitz sign and occasionally the presence of a Woronoff's ring. Additionally, patients often experience pain, itch, burning and bleeding from the lesions. The size of single lesions varies from pinpoint to plaques that cover large areas of the body and vary over time. Although psoriasis is a chronic disease, periods of complete remission do occur.

Other types of psoriasis are less common and include guttate, erythrodermic, inverse, palmoplantair and generalized pustular psoriasis. In about half of the psoriasis patients the nails are involved showing signs of pitting, onycholysis (nail plate separation), oil spots and/or dystrophy. Psoriatic nail disease seems to occur more often in patients with psoriatic arthritis. This inflammatory type of arthritis has a prevalence among patients with psoriasis ranging from 6% to 39%, but is likely to be clinically relevant in about 10% of patients.[28] Psoriatic arthritis is a seronegative arthritis that most often presents as an oligoarticular disease with interphalangeal arthritis but it may also present as a spondylarthropathy.

1.4 Psoriasis therapies

Although a range of topical and systemic therapies are available for the treatment of psoriasis that focus on disease control, there is no definite cure for psoriasis. Therapies are therefore aimed at inducing remission and/or making the extent of psoriasis tolerable for the patient because it is not always realistic to induce complete clearance. The selection of an appropriate therapy or combination of therapies depends on multiple factors[29]: (1) psoriasis related factors; type, severity, extensiveness, disease duration, localisation; (2) treatment related factors; effectiveness, short and long term, reversible and irreversible side effects, contra-indications, comorbidities, availability, duration of remission, previous therapies; (3) patient related factors; age, gender, physical and mental health, patient's preference and adherence to therapy.

Topical therapies

Topical therapies are generally suitable for mild or localized psoriasis or can be used in combination with phototherapy or a systemic therapy to enhance their efficacy or reduce cumulative exposure of these therapies. Topical corticosteroids class 2-4 and vitamin D analogues are among

the most frequently prescribed therapies for psoriasis. A treatment will usually start with a topical corticosteroid 1 or 2 times daily or calci(po)triol 2 times daily, a combination(preparation) of these therapies may even provide better response rates and is steroid sparing. Other options are short-contact anthralin treatment especially in case of a few large plaques or coal tar products within a day care setting for more generalized disease. Tacrolimus and pimecrolimus have been suggested as possible therapeutic options for intertriginous and facial psoriasis.

Photo(chemo)therapy

Narrowband UVB and psoralen with ultraviolet-A (PUVA) and are generally positioned as a second line therapy in between topical and systemic therapy.[29-31] Its anti-psoriatic effect is mainly based on the UV-induced immune suppression, although various biological effects have been described.

UVB is available in both broadband and narrowband, but because of the increased effectiveness and good tolerability narrowband phototherapy is usually preferred. The UVB dosing is based on the minimal erythemogenic dose (MED) and skin type and patients are generally treated 3 times a week until remission is induced. PUVA is given as a combination treatment of UVA and photosensitizing psoralen (8-MOP) which can be administered systemic (oral) as well as topical bath and cream PUVA. The dosing is also based on the MED and skin type with a usual dosing frequency of 2 times weekly until the induction of remission. Approximately three-quarters of all patients treated with phototherapy attained at least a PASI 75 response after 4 to 6 weeks, and clearance was frequently achieved.[31]

The most common side effect is UV-erythema from overexposure. At the long term high cumulative UV doses lead to premature aging of the skin and an increased risk of skin cancer. The PUVA induced skin cancer risk increases exponentially after 250 treatments and is persistent after discontinuation of therapy.[32] Exposure to 300 or more UVB therapies is also significantly associated with squamous cell carcinoma (SCC) risk but is about one seventh of the carcinogenicity of PUVA.[33] When a patient subsequently also uses cyclosporine, this carcinogenic risk is even stronger, which is probably due to decreased cutaneous immuunsurveillance. In the 'PUVA Follow Up Study', SCC risk increased 8 folds in psoriasis patients who used cyclosporine after having had 200 or more PUVA treatments compared to those not using cyclosporine.[34] These long-term side effects of photochemotherapy make it therefore unsuitable as a long-term treatment and both the Dutch and European guidelines on the systemic treatment of psoriasis vulgaris consider previous high dose PUVA therapy as a relative contraindication for cyclosporine.[29, 31] Based on comparable efficacy and less carcinogenic side effects, UVB is therefore generally preferred over PUVA therapy.[29, 31]

Systemic therapies

Based on low efficacy of retinoids and few safety data on fumaric acid esters, the Dutch guideline for the treatment of moderate to severe psoriasis prefers methotrexate (MTX) and cyclosporine as oral therapies for the treatment of psoriasis. If there are no specific contraindications MTX is generally viewed as the most optimal maintenance treatment for psoriasis, since the maximum prescription duration for cyclosporine is approximately one year.

MTX is a folic acid analogue that inhibits the enzyme dihydrofolate reductase resulting in decreased synthesis of DNA and RNA. Besides the antiproliferative effects on T cells and keratinocytes MTX also has immunomodulating effects, which are considered the main mechanisms of action. MTX is widely employed in Europe for the treatment of moderate to severe plaque psoriasis and psoriatic arthritis as well. Partial remission with MTX was reported to be 60% and PASI 90 occurred among 40% of patients after 16 weeks of treatment.[31] The two most important adverse drug reactions associated with MTX therapy are myelosuppression and hepatotoxicity (especially among patients who consume large amounts of alcohol), which require appropriate screening and monitoring procedures. Among the relative contraindications are congestive heart failure, diabetes mellitus and colitis ulcerosa, which have also been associated with psoriasis.[29]

Cyclosporine selectively but reversibly inhibits the proliferation of T lymphocytes and the production and release of cytokines. Its position is mainly suggested as an induction therapy in adults with moderate to severe psoriasis, showing a partial remission of 86% after 16 weeks of 5 mg/kg per day.[31] The most important adverse drug reactions are nephrotoxicity, increase in blood pressure and the increased risk of malignancies, especially of the skin. Among the absolute contraindications are insufficiently controlled arterial hypertension, severe infectious disease and previous potential carcinogenic therapies like PUVA >1000 J/cm^2.[31]

Acitretin has antiproliferative and immunomodulatory properties including inhibition of the IL-6 driven induction of Th 17 cells. However, due to the relatively low efficacy (i.e. clear or compete improvement in 41% or less) it is not suggested as a first choice monotherapy for the treatment of psoriasis.[29] Among the absolute contraindications are hepatitis and excessive alcohol abuse and relative contraindications are diabetes mellitus, (drug controlled) hyperlipidaemia and arteriosclerosis.[31]

Fumaric acid esters inhibit the proliferation of keratinocytes and favourably affect the Th1/Th2 balance in psoriasis. It is an effective therapy showing a PASI 75 response among 50% to 70% of the patients after 16 weeks.[29] This therapy is nevertheless not registered in the Netherlands and is therefore used as an off-label therapy for psoriasis. One of the contraindications is severe diseases of the gastrointestinal tract and/or the kidneys.[29]

The biologics that are currently registered in the Netherlands for the treatment of psoriasis include TNF-alpha antagonists (i.e. adalimumab, etanercept and infliximab) and ustekinumab, which targets the common p40 subunit of interleukin-12/23. Some of these more targeted therapies may be more effective than conventional systemic therapies with a PASI 75 response varying from approximately 50% for etanercept at the maximum dosing to approximately 80% for infliximab after 3 months of anti-TNF-alpha antagonists[31] and almost 70% showing a partial response after 3 months of ustekinumab.[35] The presence of infections or a history of recurrent infections are contraindicated for all biologics and congestive heart failure is especially contra-indicated for adalimumab and infliximab.[31] As for other immunosuppressive drugs, the risk of (haematological) malignancies and serious infections (including tuberculosis) is likely to be increased among patients exposed to these drugs as is illustrated by the recent withdrawal of efalizumab (i.e. a biological for psoriasis). For now, no phase IV postmarketing safety studies have been performed to assess these risks.

1.5 Psoriasis as a problem

Psoriasis has been considered a challenging disease from several points of view such as the patient, health care providers and health insurance companies. Although issues may differ between these groups, some problems related to safety of therapies and costs are relevant to all.

Psoriasis can have a major impact on the patient's health related quality of life (HRQOL) causing higher levels of anxiety, depression, worry and even suicidal thoughts.[36] The reduced physical and mental functioning associated with psoriasis is even comparable to that observed in patients with cancer, arthritis, heart disease, diabetes and depression.[36] However, the impact on the HRQOL is not directly related with the severity of the skin symptoms: patients with mild disease from a clinical perspective may report substantial HRQOL impairment. Interestingly, psoriasis related HRQOL impairment did not change significantly in time suggesting that its impact is stable and that it remains a difficult disease to cope with.[37] Anti-psoriatic treatments may provide temporary relief, but a survey among psoriasis patients found that none of the prior mentioned traditional systemic therapies were highly satisfactory.[38] Clinical trials suggest that the degree of clinical response to a therapy has a linear relationship to the patients' HRQOL improvement. It is suggested that in order to have a substantial impact on HRQOL the improvement in skin clearance needs to be substantial (i.e. ≥PASI 75) and the strongest HRQOL improvements were measured in those subjects with a PASI response of 90% or more.[39] Ideally, the ultimate treatment goal in patients with psoriasis would be complete clearance, but achieving a positive risk:benefit ratio from a physician's and patient's perspective is more realistic.

In the process of selecting a suitable therapy for a patient with psoriasis, a clinician should be able to make a well-founded decision between the various options. Due to the chronic nature of psoriasis, a therapy should be safe and effective in long-term use to have a meaningful impact on the patient's clinical course. Generally it can be considered that therapies with a more rapid onset and substantial improvement of the skin may also have the potential of more serious side-effects.

The skin cancer inducing effects of therapies such as cyclosporine and PUVA for example limit these therapies as long term treatment options, an effect that is even stronger when these treatments are subsequently given within the same patient.[2, 32] The risk of malignancy associated with biologics is still unclear and most data comes from rheumatoid arthritis (RA) patients. One meta-analysis reported a significantly increased risk of solid tumours in RA patients receiving anti-TNF-α compared to subjects using placebo predominantly within a few months after the start of treatment[40], while other studies could not confirm an overall increased risk of cancer associated with anti-TNF-alpha.[41] Possible explanations for these different findings are the different distributions of risk factors for cancer such as life style factors and prior therapies. Additionally, psoriasis may also have an increased intrinsic risk for malignancies which can make it even more difficult to assess the effect of the various therapies.[42] The scarcity of the literature on the safety of biologics in psoriatic patients and the potential cumulative effects of multiple anti-psoriatic therapies require an international registry of post-marketing surveillance studies to monitor the effectiveness and safety of systemic agents which have been initiated by the Italians in the Psonet collaboration.[43]

The higher likelihood of infections due to immunosuppressive or immunomodulatory anti-psoriatic therapies are another point of concern when selecting a therapy. Basic research showed that psoriasis patients have an increased epidermal barrier function with more anti-microbial peptides which may be protective against infections, although its clinical relevance on the baseline risk of infections has not been sufficiently investigated.[26] Studies of patients with RA suggest that since the introduction of anti-TNF-alpha antibody therapies the occurrence of severe infections including tuberculosis has increased.[40, 44] Excluding latent TB prior to therapy initiation and follow up of infectious signs are therefore important in all patients on immunosuppressive drugs, including psoriasis patients.

Limited and conflicting data on the safety of therapies in psoriasis can make it complex to select the appropriate therapy. This also emphasises the importance of regularly updated evidence based treatment guidelines. It would be valuable to both patients and health care professionals to know the baseline risk of important comorbidities such as infections, malignancies and cardiovascular diseases in patients with psoriasis as well as the anti-psoriatic drug related risks.

Besides the safety of anti-psoriatic therapies their associated costs are another issue. Psoriasis may pose a significant economic burden to society. The direct costs include the use of antipsoriatic drugs, medical care and also drugs for treating comorbidities. Since the introduction of the biologics the associated costs have likely increased in the last years, although improved therapeutic effects may have also reduced the need for expensive inpatient treatments. Additionally, the generally increased healthcare consumption of psoriasis patients also has its effect on direct costs by higher detection and treatment rates of comorbidities. No data are yet available of the current impact psoriasis on the Dutch healthcare budget.

1.6 Aims of this thesis

Comorbidity in psoriasis patients

Various dermatological diseases including psoriasis have been associated with comorbidities. This thesis starts with an overview of comorbidities in dermatology, the complexity and multifactorial aspects of these associations and their clinical relevance (*chapter 2*). Most research on comorbidities has been conducted among patients with psoriasis, especially on its association with cardiovascular comorbidities. We therefore conducted a review of the literature on cardiovascular risk factors in psoriasis and the possible hypotheses underlying this association (*chapter 3*).

To investigate whether patients with psoriasis actually have a different risk of cardiovascular diseases we used Dutch hospital and pharmacy linked databases (PHARMO RLS). Our first aim was to compare the prevalent use of metabolic drugs in psoriasis patients and a large sample of the general population (*chapter 4*). This was followed by a large population based cohort study that investigated a clinically relevant outcome, that is hospitalization because of ischemic heart diseases, in psoriasis patients and compared it to a matched reference cohort (*chapter 5*).

Despite its relevance, only little is known about the baseline risk of infectious diseases in patients with psoriasis. The same databases were for that reason also used to assess the baseline risk of infectious diseases in psoriasis patients (*chapter 6*). However, the association between psoriasis and comorbidities remains complex making it difficult to investigate (*chapter 7*).

The treatment of psoriasis patients

Evidence based guidelines become more and more important in the treatment of patients including those with psoriasis. The implementation of the Dutch guidelines for the treatment of moderate to severe plaque psoriasis available since 2003 among dermatologists was evaluated

in *chapter 8*. This was followed by a report of the survey among Dutch dermatologists on the reimbursement criteria for biological therapies for psoriasis in the Netherlands (*chapter 9*). *Chapter 10* describes the relevance of post-marketing effectiveness and safety studies in the treatment of psoriasis. Finally, *chapter 11* provides a general discussion of the findings within a broader perspective.

References

1. Naldi L. Epidemiology of psoriasis. Curr Drug Targets Inflamm Allergy 2004;3(2):121-8.
2. Stern RS, Nijsten T, Feldman SR, Margolis DJ, Rolstad T. Psoriasis is common, carries a substantial burden even when not extensive, and is associated with widespread treatment dissatisfaction. J Investig Dermatol Symp Proc 2004;9(2):136-9.
3. Nevitt GJ, Hutchinson PE. Psoriasis in the community: prevalence, severity and patients' beliefs and attitudes towards the disease. Br J Dermatol 1996;135(4):533-7.
4. Henseler T, Christophers E. Psoriasis of early and late onset: characterization of two types of psoriasis vulgaris. J Am Acad Dermatol 1985;13(3):450-6.
5. Nijsten T, Looman CW, Stern RS. Clinical severity of psoriasis in last 20 years of PUVA study. Arch Dermatol 2007;143(9):1113-21.
6. Kurd SK, Gelfand JM. The prevalence of previously diagnosed and undiagnosed psoriasis in US adults: results from NHANES 2003-2004. J Am Acad Dermatol 2009;60(2):218-24.
7. Hoffman C, Rice D, Sung HY. Persons with chronic conditions. Their prevalence and costs. Jama 1996;276(18):1473-9.
8. Stern RS. Inpatient hospital care for psoriasis: a vanishing practice in the United States. J Am Acad Dermatol 2003;49(3):445-50.
9. Finlay AY, Coles EC. The effect of severe psoriasis on the quality of life of 369 patients. Br J Dermatol 1995;132(2):236-44.
10. Krueger G, Koo J, Lebwohl M, Menter A, Stern RS, Rolstad T. The impact of psoriasis on quality of life: results of a 1998 National Psoriasis Foundation patient-membership survey. Arch Dermatol 2001;137(3):280-4.
11. Fowler JF, Duh MS, Rovba L, et al. The impact of psoriasis on health care costs and patient work loss. J Am Acad Dermatol 2008;59(5):772-80.
12. Piskin G, Sylva-Steenland RM, Bos JD, Teunissen MB. In vitro and in situ expression of IL-23 by keratinocytes in healthy skin and psoriasis lesions: enhanced expression in psoriatic skin. J Immunol 2006;176(3):1908-15.
13. Bos JD, Hulsebosch HJ, Krieg SR, Bakker PM, Cormane RH. Immunocompetent cells in psoriasis. In situ immunophenotyping by monoclonal antibodies. Arch Dermatol Res 1983;275(3):181-9.
14. Griffiths CE, Powles AV, McFadden J, Baker BS, Valdimarsson H, Fry L. Long-term cyclosporin for psoriasis. Br J Dermatol 1989;120(2):253-60.
15. Gottlieb SL, Gilleaudeau P, Johnson R, et al. Response of psoriasis to a lymphocyte-selective toxin (DAB389IL-2) suggests a primary immune, but not keratinocyte, pathogenic basis. Nat Med 1995;1(5):442-7.
16. Krueger G, Ellis CN. Psoriasis--recent advances in understanding its pathogenesis and treatment. J Am Acad Dermatol 2005;53(1 Suppl 1):S94-100.
17. Eyre RW, Krueger GG. Response to injury of skin involved and uninvolved with psoriasis, and its relation to disease activity: Koebner and 'reverse' Koebner reactions. Br J Dermatol 1982;106(2):153-9.
18. Fry L, Baker BS. Triggering psoriasis: the role of infections and medications. Clin Dermatol 2007;25(6):606-15.
19. Leung DY, Travers JB, Norris DA. The role of superantigens in skin disease. J Invest Dermatol 1995;105(1 Suppl):37S-42S.
20. Nickoloff BJ, Wrone-Smith T. Superantigens, autoantigens, and pathogenic T cells in psoriasis. J Invest Dermatol 1998;110(4):459-60.
21. Nestle FO, Kaplan DH, Barker J. Psoriasis. N Engl J Med 2009;361(5):496-509.

22. Andressen C, Henseler T. [Inheritance of psoriasis. Analysis of 2035 family histories]. Hautarzt 1982;33(4):214-7.
23. Farber EM, Nall ML. Natural history and genetics. Psoriasis, 3rd edn New York: Marcel Dekker 1998:107-58.
24. Trembath RC, Clough RL, Rosbotham JL, et al. Identification of a major susceptibility locus on chromosome 6p and evidence for further disease loci revealed by a two stage genome-wide search in psoriasis. Hum Mol Genet 1997;6(5):813-20.
25. de Cid R, Riveira-Munoz E, Zeeuwen PL, et al. Deletion of the late cornified envelope LCE3B and LCE3C genes as a susceptibility factor for psoriasis. Nat Genet 2009;41(2):211-5.
26. Hollox EJ, Huffmeier U, Zeeuwen PL, et al. Psoriasis is associated with increased beta-defensin genomic copy number. Nat Genet 2008;40(1):23-5.
27. Griffiths CE, Barker JN. Pathogenesis and clinical features of psoriasis. Lancet 2007;370(9583):263-71.
28. Myers WA, Gottlieb AB, Mease P. Psoriasis and psoriatic arthritis: clinical features and disease mechanisms. Clin Dermatol 2006;24(5):438-47.
29. CBO. Nederlandse Verenigung voor Dermatologie en Venerologie (NVDV) and Institute for Healthcare Improvement (CBO). Dutch Guideline for the treatment of severe psoriasis (ultraviolet B, ultraviolet A in combination with oral psoralen, cyclosporin A, methotrexate and acitretine). Alphen aan den Rijn: Van Zuiden Communications B.V. ; 2003.
30. Nast A, Kopp I, Augustin M, et al. German evidence-based guidelines for the treatment of Psoriasis vulgaris (short version). Arch Dermatol Res 2007;299(3):111-38.
31. Pathirana D, Ormerod A, Saiag P, et al. European S3-Guidelines on the systemic treatment of psoriasis vulgaris. J Eur Acad Dermatol Venereol 2009;23(s2):1-70.
32. Nijsten TE, Stern RS. The increased risk of skin cancer is persistent after discontinuation of psoralen+ultraviolet A: a cohort study. J Invest Dermatol 2003;121(2):252-8.
33. Lim JL, Stern RS. High levels of ultraviolet B exposure increase the risk of non-melanoma skin cancer in psoralen and ultraviolet A-treated patients. J Invest Dermatol 2005;124(3):505-13.
34. Marcil I, Stern RS. Squamous-cell cancer of the skin in patients given PUVA and ciclosporin: nested cohort crossover study. Lancet 2001;358(9287):1042-5.
35. Leonardi CL, Kimball AB, Papp KA, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). Lancet 2008;371(9625):1665-74.
36. Rapp SR, Feldman SR, Exum ML, Fleischer AB, Jr., Reboussin DM. Psoriasis causes as much disability as other major medical diseases. J Am Acad Dermatol 1999;41(3 Pt 1):401-7.
37. Unaeze J, Nijsten T, Murphy A, Ravichandran C, Stern RS. Impact of psoriasis on health-related quality of life decreases over time: an 11-year prospective study. J Invest Dermatol 2006;126(7):1480-9.
38. Nijsten T, Margolis DJ, Feldman SR, Rolstad T, Stern RS. Traditional systemic treatments have not fully met the needs of psoriasis patients: results from a national survey. J Am Acad Dermatol 2005;52(3 Pt 1):434-44.
39. Reich K, Griffiths CE. The relationship between quality of life and skin clearance in moderate-to-severe psoriasis: lessons learnt from clinical trials with infliximab. Arch Dermatol Res 2008;300(10):537-44.
40. Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. Jama 2006;295(19):2275-85.
41. Carmona L, Descalzo MA, Perez-Pampin E, et al. All-cause and cause-specific mortality in rheumatoid arthritis are not greater than expected when treated with tumour necrosis factor antagonists. Ann Rheum Dis 2007;66(7):880-5.

42. Gelfand JM, Berlin J, Van Voorhees A, Margolis DJ. Lymphoma rates are low but increased in patients with psoriasis: results from a population-based cohort study in the United Kingdom. Arch Dermatol 2003;139(11):1425-9.
43. Psonet. http://www.psonet.eu/. Last accessed december 2009.
44. Kroesen S, Widmer AF, Tyndall A, Hasler P. Serious bacterial infections in patients with rheumatoid arthritis under anti-TNF-alpha therapy. Rheumatology (Oxford) 2003;42(5):617-21.

Chapter 2

Comorbidities in dermatology

M. Wakkee
T. Nijsten

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Abstract

Recently, comorbidities have been re-discovered in dermatology. Although numerous associations between skin diseases and other conditions have been reported, only a few are well documented. The association of comorbidities and dermatoses is complex and multifactorial. Lifestyle factors, impaired health-related quality of life and depression, therapeutic interventions and several biases may confound the relationship between skin diseases and comorbidities. This review discusses observational studies that assess comorbidities in psoriasis, atopic dermatitis, vitiligo and nonmelanoma skin cancer, the likelihood of the observed associations and their clinical consequences.

Introduction

There is no universally accepted definition for the term comorbidity. Traditionally, comorbidity has been defined as a medical condition coexisting with the primary disease either as a current or past condition.[1] Wikipedia defines comorbidity as the "the effect of all other diseases an individual patient might have other than the primary disease of interest".[2] Comorbidities should be distinguished from diseases with a common immunologic pathogenesis (eg, mixed connective tissue diseases and related skin conditions) or dermatoses strongly associated with specific (internal) diseases (eg, erythema nodosum and sarcoidosis or inflammatory bowel disease).

The association between dermatologic diseases and comorbidities is often complex and multifactorial making it difficult to demonstrate direct relationships (Fig. 1). Life style factors, impaired health-related quality of life, depression, therapeutic interventions, and varying use of medical care may confound an association between a skin disease and comorbidity. Also, several biases, such as detection bias (ie, patients with a skin disease are more likely to be diagnosed with another disease while visiting their physician for their dermatosis) may affect observational studies results.

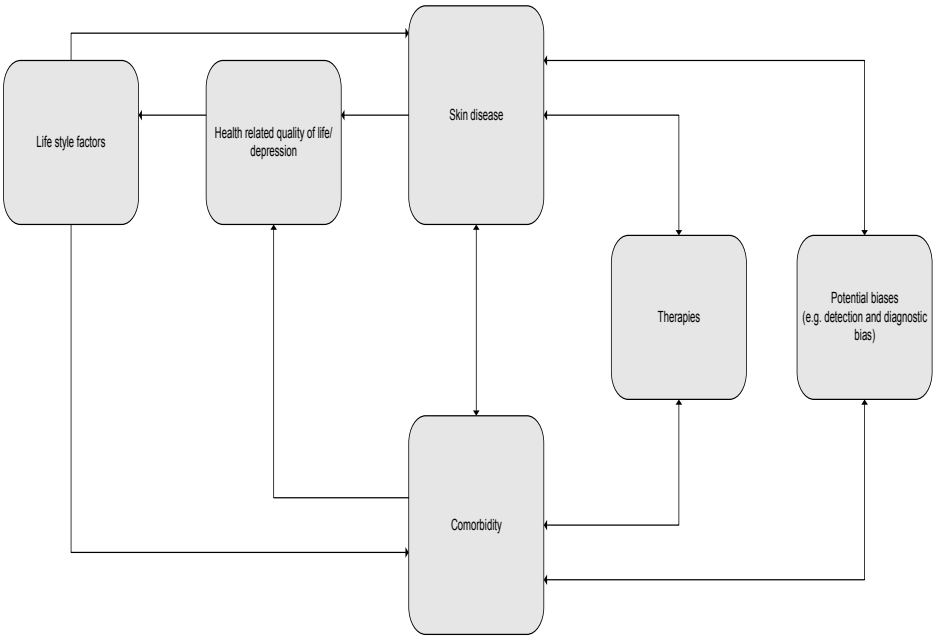

Figure 1. The complex relationship between dermatological diseases and comorbidities.

The presence of comorbidities in dermatology is of interest for various reasons. From a preventative perspective, a skin disease can be an early marker of systemic disease, and therefore, identify patients who are at risk of having other, more life-threatening diseases. An association between a skin disease and comorbidities may influence clinical management (eg, multidisciplinary approach and treatment options). Ideally, treatments are selected that improve both conditions simultaneously. However, comorbidities may also be a contra-indication for therapies indicated for the skin disease or drugs used in the treatment of the comorbidity may interact with the dermatologic therapy.

Comorbidities impact health-related quality of life (HRQOL) in patients with a dermatologic condition.[3] Knowledge about the association between a dermatosis and another disease may increase the understanding of the shared pathogenesis of both diseases.

The objective of this review is to provide an overview of comorbidities in dermatology. The focus will be on direct and indirect (eg, therapy or life-style related) associations, the likelihood of the association, and possible consequences in daily practice.

Psoriasis

Most research on comorbidities in dermatology has been conducted among patients with psoriasis.[4] Psoriatic arthritis, cardiovascular diseases or the metabolic syndrome, malignancies, infections, auto-immune diseases, and depression are all associated with psoriasis.

Psoriatic arthritis

A well-known comorbidity in psoriasis is psoriatic arthritis (PsA). The prevalence among patients with psoriasis varies from 6% to 40%, depending on the population studied, but is likely to be about 10%.[5] PsA is a seronegative spondylarthropathy and there are five subtypes: arthritis of the distal interphalangeal joints, asymmetric oligoarthritis, symmetric polyarthritis, spondylitis, and arthritis mutilans.[6] The joint complaints generally occur 7- to 10-years after the onset of psoriasis, but may also present themselves without cutaneous signs of psoriasis in about 10% of the cases. Patients with early onset psoriasis, severe disease, nail changes, and pustular types of psoriasis have the highest likelihood of developing PsA. No serologic marker exists for PsA. The simplest and frequently used diagnostic criteria for PsA includes the presence of inflammatory arthritis, psoriasis, and the absence of serologic tests for rheumatoid factor.[6] More recently, the more specific Classification criteria for Psoriatic Arthritis (CASPAR) have been introduced, which also included features such as family history of psoriasis, nail dystrophy, and juxta-articular new bone formation.[7] Most importantly, PsA is diagnosed by excluding other forms of seronegative

arthritis (ie, absence of serum markers such as rheumatoid factor).[8] PsA can result in extensive irreversible joint damage[9] that may be prevented by early detection and treatment.[10, 11]

Cardiovascular disease

Psoriasis is a chronic inflammatory skin disorder in which many different inflammatory cells are involved. T-lymphocytes play a major role in this network, predominantly releasing type 1 cytokines, such as interferon-gamma, tumor necrosis factor-alpha, and interleukin-2, at the site of inflammation.[12] These cytokines further stimulate T-lymphocyte proliferation, the production of cytokines by T-lymphocytes and macrophages, chemokine release from macrophages, and the expression of adhesion molecules on vascular endothelial cells. The inflammation leads to oxidative stress that may result in systemic consequences.[13] High levels of oxidants stimulate the formation of atherosclerotic lesions in the vessel walls that may lead to a higher cardiovascular disease risk.

Cardiovascular diseases and the metabolic syndrome, which comprises the presence of three, or more, of five cardiovascular risk factors, such as obesity, increased cholesterol and triglycerides, hypertension, and glucose intolerance, have recently recaptured the attention in psoriasis research. As early as 1973, an increased prevalence of occlusive vascular disease among psoriasis inpatients compared with other dermatologic inpatients (11.5% versus 5.0%) was reported.[14] In 1986, a Swedish cross-sectional study suggested an association between psoriasis and hypertension, but this was not confirmed in a large, United States, prospective cohort study.[15, 16] Another Swedish study demonstrated a 50% greater risk of death from cardiovascular disease, among patients who were treated at least once as a psoriasis inpatient, compared with the general population.[17] In contrast, the overall risk for cardiovascular death was slightly decreased among outpatients with psoriasis (standardized mortality ratio = 0.94; 95% Confidence Interval [CI] 0.89-0.99). The findings that hospitalized patients with psoriasis, especially those severely affected, are at increased risk, were confirmed in a German retrospective- cohort study of 581 cases and an Italian case control study including 338 patients.[18, 19] Two prospective, populationbased cohort studies from the United Kingdom and the United States demonstrated that patients with psoriasis have higher risks of myocardial infarction, angina, atherosclerosis, peripheral vascular diseases, and stroke.[20, 21] The relative risk for myocardial infarction was greatest among young patients with severe psoriasis; a 30-year old patient with severe psoriasis had an adjusted relative risk of 3.10 (95% CI 1.98-4.86) for myocardial infarction compared with the general population. From this same UK General Practice Research Database (GPRD), a study showed a strong association between severe psoriasis and cardiovascular risk factors like diabetes, hypertension, hyperlipidemia, obesity, and smoking.[22] After adjusting for the available information on traditional cardiovascular risk factors, these associations persisted in case of diabetes (Odds Ratio [OR] = 1.62; 95% CI 1.30-2.01), smoking (OR = 1.31; 95% CI 1.17-1.47), and an increased body mass index (OR

for BMI>30 = 1.79; 95% CI 1.55-2.05). In a large prospective cohort study of almost 80,000 United States nurses, increased measures of adiposity (waist circumference, hip circumference, and waist- to hip ratio), and weight gain were strong risk factors for incident psoriasis, suggesting that weight gain precedes the development of psoriasis, which is consistent with the findings of an Italian case control study.[23, 24]

Two recent population based database studies that included pharmacy data did not confirm the association between psoriasis and treatment of cardiovascular disease. In a study using the data from the UK GPRD, patients with psoriasis were not more exposed to antihypertensive drugs before diagnosis of psoriasis.[25] In a Dutch population-based study using a pharmacy database, the 5-year prevalence exposure of cardiovascular and antidiabetic drugs were compared between patients with psoriasis and controls.[26] This study showed that patients with psoriasis were significantly more likely to have used antihypertensives, anticoagulant and antiplatelet agents, digoxin, nitrates, lipid lowering and antidiabetic drugs. However, after adjusting for the number of unique drugs used in the history, which were used as a proxy for the consumption of health care, psoriasis was no longer associated with any of these drug classes suggesting that medical surveillance bias may have affected the study findings.

In summary, most but not all epidemiologic studies suggest that patients with psoriasis are at increased risk of cardiovascular disease. The absolute risk increase seems to be modest (about 20% to 30%) compared with the baseline risk in the general population. However, it remains challenging to differentiate whether the risk is due to the chronic inflammatory status of patients with psoriasis or other factors, such as different lifestyles, impaired HRQOL, prior drug exposures, and increased medical surveillance (Fig. 1). Prospective observational studies, including patients with incident psoriasis and all possible confounders, or randomized clinical studies are warranted to further explore the important association between psoriasis and cardiovascular disease.

The clinical implications for the current care of patients with psoriasis have been discussed among a group of experts in the United States.[27] Their advice was to follow the recommendations of the American Heart Association to screen for risk factors from as early as age 20, to repeat this at least once every 2 years from age 40, and to advise lifestyle modifications as first-line therapy when appropriate.

Malignancies

Several epidemiologic studies have suggested that patients with psoriasis are significantly more likely to develop nonmelanoma skin cancer (NMSC), lymphoma, and cancer of the lung, larynx, pharynx, liver, pancreas, female breast, vulva, penis, bladder and kidney.[28-30] Although

chronic inflammation of the skin may decrease the risk of skin cancer because of increased cutaneous immunosurveillance, the incidence of squamous cell carcinoma (SCC), and to a lesser extent basal cell carcinoma (BCC), is increased in patients with psoriasis. This increased risk of NMSC seems primarily related to carcinogenic treatment exposures, such as high-dose psoralen plus ultraviolet A (PUVA), and to a lesser extent, of UVB.[31] The antipsoriatic therapy cyclosporine, especially after PUVA exposure, increases the risk of NMSC. The PUVA follow-up study showed an increased risk of melanoma in patients treated with PUVA, which is greater in patients exposed to high doses of PUVA and increases with the passage of time.[32] The carcinogenicity of coal tar has been shown in animal studies and in occupational settings.[33] Whether dermatologic use of coal tar as a monotherapy actually increases the risk of skin tumors and other malignancies is unknown. In addition to agents used for psoriasis treatment, psoriasis has been associated with life-style factors, such as increased alcohol consumptionand smoking, that are risk factors for oral cavity, esophagus, liver, pancreas, lung, kidney and breast cancer.[34] Two large cohort studies that followed up inpatients with psoriasis confirmed smoking and alcohol-related causes of death led to excess mortality.[28, 35]

Several studies suggest an association between psoriasis and lymphoma with increasing risks for those severely affected by psoriasis.[28, 36, 37] A population-based study using the UK GPRD demonstrated an increased risk of about a third of developing any kind of lymphoma. The highest relative risks were observed for cutaneous T-cell lymphoma (adjusted relative risk=4.34 [95% CI 2.89-6.52]).[36, 37] Caution is needed in the interpretation of these findings because the exposure to psoriasis therapies that may increase the risk of lymphoma (eg, cyclosporine and methotrexate) were not assessed and the results may have been affected by a misclassification bias (ie, patients having cutaneous T-cell lymphoma may have initially been misdiagnosed with psoriasis resulting in false positive psoriasis cases with a lymphoma). In a prospective cohort of 1380 patients treated with PUVA, only those with 36 months or more exposure of methotrexate developed significantly more lymphomas than expected (incidence rate ratio = 4.39; 95% CI, 1.59-12.06).[38] The possible effect of psoriasis therapies on the development of hematological malignancies is also suggested by a postmarketing study of cyclosporine.[39] Although the available studies suggest patients with psoriasis are at an increased risk of hematological malignancies, this association might be explained by an increased baseline risk, prior drug use, or misclassification. Further documentation about the baseline risk of lymphomas in patients with psoriasis would be valuable because biological therapies might increase lymphoma risk in this population.[40]

Infections

Several micro-organisms have been associated with provoking or exacerbating psoriasis. The strongest evidence exists for the induction of guttate psoriasis by a tonsillar Streptococcus

pyogenes infection. The first case report of this association was published more than a century ago and more than 50 years ago, a study reported that in two thirds of patients with guttate psoriasis, there is a history of an acute sore throat 1- to 2-weeks before the eruption and serologic evidence of a recent streptococcal infection.[41] This observation has been confirmed by several other studies and some indicate that streptococcal throat infections can also cause exacerbation of chronic plaque psoriasis.[42]

An Austrian study showed that patients colonized with the toxin-positive S. aureus had a significantly higher psoriasis area and severity index score than patients with toxin negative S. aureus or without bacterial colonization.[43] In practice, secondary infections of chronic psoriasis plaques are rarely seen. This was confirmed by a large epidemiologic study on disease concomitance in psoriasis, which revealed that patients with psoriasis have an increased resistance to bacterial and viral infections compared with controls and patients with atopic dermatitis.[44] Approximately 30% of patients with atopic dermatitis suffered from either bacterial or viral infections, while this complication occurred in 7% of patients with psoriasis. These results may be related to the increased expression of antimicrobial peptides and proteins (AMPs) in psoriatic skin.[45, 46] AMPs are involved in the innate defense against bacterial infections and clinical expression of these natural antibiotics correlate with the susceptibility to skin infections.

Psoriasis is associated with an increased betadefensin genomic copy number.[47] Beta-defensins have broad-spectrum antimicrobial activities and proinflammatory properties. The variation in gene dosage may affect the development of infections and inflammatory diseases, which can contribute to the psoriasis susceptibility and the low prevalence of skin infections.

In contrast to cutaneous infections, systemic infections in patients with psoriasis are not well documented. A large Swedish population-based cohort study, which followed patients for a decade, found significantly more hospitalizations for pneumonia and systemic viral infections among patients with psoriasis compared with the general population, without taking systemic therapy exposure into consideration.[15] A few small retrospective case series that assessed postoperative infections after orthopedic surgery in patients with psoriasis have shown inconsistent findings: a case control study showed that 18% (15/85) of patients with postoperative infections had psoriasis and only 1% (2/202) of those without infections and concluded that psoriasis is a risk factor for postoperative infections after hip replacement surgery, but not for knee prosthesis.[48] Otherwise, severe immunodeficiency in human immunodeficiency virus (HIV) may also trigger or exacerbate psoriasis.[49] The manifestations of psoriasis in patients with HIV vary. Usually it presents itself as the first clinical manifestation of HIV, although it can also appear in the advanced stages of HIV when it has progressed to AIDS.[50] The pathogenesis of psoriasis in HIV disease is not fully understood, but among Chinese patients with HIV, a significant association was found with the HLA-Cw*0602 allele.[51] Immune reconstitution by effective

antiretroviral therapy has shown to significantly improve psoriasis.[52] Immunosuppressive or immunomodulatory antipsoriatic therapies also increase the risk of systemic infections in patients with psoriasis. Methotrexate has been reported to cause reactivation of latent tuberculosis (TB) infection when used for the treatment of psoriasis. For cyclosporine, the development of TB has only been described in patients with transplants exposed to high doses of this drug.[53, 54] Since the introduction of anti-TNF antibody therapies, several studies showed an increased risk of severe infections in these patients, of which tuberculosis is one of the most important.[40, 55] Excluding latent TB and follow up of infectious signs is important in patients on immunosuppressive drugs, including the biologics. Evidence-based medicine on the role of vaccinations in patients with psoriasis using immunosupressants is still limited. A recent consensus statement, based on the available literature and expert opinions, advices standard vaccination before therapy initiation and annual inactivated influenza vaccine for patients on biologic agents until more long-term, follow-up evidence is available.[56] Live or live-attenuated vaccines should be avoided once one of these therapies has been initiated.

Others

A case-control study among 136 patients with inflammatory bowel diseases showed that psoriasis was more common among relatives of patients than in the controls (9.6% versus. 2.2%), which may be due to the genetic linkage with HLA B27 of these disorders.[57] The association between asymptomatic celiac disease and psoriasis remains controversial, which may be because of the high prevalence of antigliadin antibodies in the general population, or low specificity of these antibodies compared with those directed against transglutaminase.[58-60] A case-control study that included more than 12,500 patients with psoriasis, suggested that after adjusting for potential confounders, patients with psoriasis were about 25% more likely to develop chronic obstructive pulmonary disease than their matched controls.[61] Other diseases, such as gout or fatty liver disease, may primarily be caused by altered lifestyle factors.

Atopic dermatitis

Asthma and allergic rhinitis

The clinical signs of atopic dermatitis are frequently a harbinger of a well-described sequence of other atopic disorders, such as asthma and allergic rhinitis, the so-called “atopic march”. These associations were confirmed in several large, well-designed longitudinal, observational studies, which provided evidence that approximately half of the patients with atopic dermatitis will develop asthma and two thirds will develop allergic rhinitis.[62] Severe atopic dermatitis and elevated serum IgE levels were found to be among the strongest risk factors for subsequent

development of these allergic comorbidities.[63, 64] Atopic diseases are also characterized by elevated IgE, peripheral and lesional eosinophilia, type 2 cytokines, epithelial dysfunction, similar allergenic triggers, and affected chromosomal regions.[65] The proposed mechanism that appears to induce the "atopic march" is epicutaneous sensitization through the barrier of disrupted skin, which induces a T helper 2 response in the skin.[66] The memory T helper 2 cells then migrate through the circulatory system to various sites, including the nasal and lung mucosa, promoting an allergic response in the airways after subsequent inhalation of these allergens.

There are studies suggesting that early intervention in atopic dermatitis with oral antihistamines might slow down the progression to allergic rhinitis and asthma.[67, 68] Data on whether early anti-inflammatory treatment prevents the onset of asthma or merely delays its onset are not available.

Infections

Skin in patients with atopic dermatitis is frequently affected by bacterial colonization and recurrent skin infections by bacterial, fungal, and viral pathogens. The high rate of S. aureus infections is related to the increased ability of this bacteria to adhere to the skin of patients with atopic dermatitis, which may be explained by skin barrier dysfunction, an increased synthesis of the extracellular matrix adhesins for S. aureus, and a deficiency in the production of endogenous antimicrobial peptides.[69, 70] In vitro studies observed that both extrinsic factors, such as cytokines and cell-autonomous differences, can influence the level of expression of genes involved in cutaneous inflammation and host defense leading to a different susceptibility for various pathogens.[71] The serotoxins secreted by S. aureus are able to penetrate the skin barrier and contribute to the persistence and exacerbation of allergic skin inflammation in atopic dermatitis. A recent systematic review suggests that there is no evidence that combined topical antibacterial and corticosteroid therapy are an effective strategy for all patients with atopic dermatitis to reduce the risk of secondary infections.[72] Prolonged antibiotic therapy may increase the prevalence of antibioticresistant strains of S. aureus.[73] As a result, in clinical practice, antibiotics are only advised in patients with atopic dermatitis with secondary bacterial infections.

Cutaneous dissemination of the herpes simplex virus on eczematous skin (ie, eczema herpeticum) is almost exclusively associated with atopic dermatitis.[74] The occurrence of eczema herpeticum in these patients is considered to be caused by a disruption of the skin barrier unmasking nectin-1, a desmosomal protein with a relevant entry receptor for herpes simplex virus, and an insufficient immune response due to the underlying predisposition to a T helper type 2 response.[75] These type 2 cytokines induce a rapid apoptosis of plasmacytoid dendritic cells and natural killer cells and down-regulate the generation of antimicrobial peptides.[74] The keystone

of eczema herpeticum treatment is prompt systemic antiviral therapy, such as acyclovir, and strict followup including eye examination and hospitalization if necessary.[74]

Malignancies

Uncertainty exists regarding the risk of cancer in patients with atopic dermatitis. It has been hypothesized that cancer risk is increased because the hyper reactive state of the immune system favors tumor onset or that cancer immunosurveillance may operate more efficiently in inflamed skin, decreasing the chance of aberrant cell proliferation. Evidence supporting the immunosurveillance theory has been reported for glioma and acute lymphoblastic leukemia (ALL). A meta-analysis of eight observational studies including a total of 3450 patients diagnosed with glioma, found a pooled relative risk for glioma of 0.69 (95% CI = 0.58 to 0.82) for patients with a history of eczema compared with patients without this condition.[76] Two large population-based casecontrol studies found a statistically significant reduced risk of between 30% to 50% for ALL in children with a history of eczema/atopic dermatitis, but this association was not confirmed in another study of 180 ALL cases.[77-79] It is unclear whether an atopic constitution or environmental factors that cause or exacerbate atopic dermatitis are responsible for the possible protective effect. Many methodological problems and possible sources of bias, including study designs, case definitions, recall bias, and the inability to analyze confounders and effect modifiers, cloud the issue.[78, 80] Some therapies, such as phototherapy and cyclosporine, may increase the risk of cancers including skin cancers, as seen in patients with psoriasis, but no good, long-term, observational data are available in this patient population. Long-term safety studies of topical calcineurin inhibitors are also lacking.

Vitiligo

Vitiligo has frequently been described in association with autoimmune diseases, particularly autoimmune thyroid diseases like Graves' disease and autoimmune hypothyroidism.[81] In a retrospective study of 293 Korean patients with autoimmune thyroid disease, 6.8% had vitiligo compared with 0.9% of controls with non-autoimmune thyroid disease and 0.8% of the healthy controls.[82] In a German cohort of 321 patients with vitiligo, a high prevalence of autoimmune thyroiditis was detected.[83] Because vitiligo can precede thyroid disease by many years, some researchers suggest regular screening for thyroid dysfunction and thyroid related autoantibodies, but the prevalence of subclinical hypothyroidism is between 4% to 10% in those without a history of thyroid diseases, questioning the usefulness of this approach.[84-87] In addition to thyroid disease, vitiligo may co-exist with other autoimmune disease like type I diabetes mellitus, pernicious anemia, Addison's disease, alopecia areata, and celiac disease, but the epidemiologic evidence for these associations is weak.[84] Combinations of these diseases are

described as autoimmune polyglandular syndromes. These genetic syndromes, especially type 1 and 3, in which autoantibodies are thought to be the cause of destruction of endocrine cells, are also associated with the presence of vitiligo. A genetic-linkage study identified a strong candidate gene, called NAPL1, contributing to a group of autoimmune and autoinflammatory diseases including vitiligo. This study demonstrated that DNA sequence variants in this region are associated with vitiligo alone, or with a more extended autoimmune phenotype, which can also comprise vitiligo.[88] Additional research is still essential on these associations and their frequency of occurrence, but informing and educating patients with regards to the signs and symptoms of these autoimmune diseases is advisable.

Nonmelanoma skin cancer

Nonmelanoma skin cancer (NMSC) is the most common cancer in Caucasians and refers to BCC and SCC. Increased childhood UV exposure is the most important risk factor of NMSC in predisposed individuals (eg, fair skin type, blond hair, and blue eyes). Recently, multiple studies have investigated comorbidities in patients with NMSC because NMSC is considered a proxy for high-UV exposure, which may relate to vitamin D levels that affect the development of several diseases and cancers (the so-called, "vitamin D hypothesis").[62, 63] A population-based cohort study of nearly 27,000 patients with SCC showed a decreased risk of colorectal cancer of 19% to 36% compared with controls without NMSC. For cutaneous melanoma, which like BCC, is more strongly related to sunburns than cumulative sun exposure, an almost two folds increased risk of breast cancer was observed in women of 60 years and older.[89] Another international- cohort study that included more than 400,000 individuals with skin cancer, observed a significantly decreased prevalence of various internal solid cancers in patients with a prior NMSC, especially in sunny countries.[64] In contrast to the protective effects of NMSC, a recent large, Swedish study detected an increased total mortality among patients with SCC partly caused by an excess rate of deaths from cancers (SMR 2.17, 95% CI 2.08-2.26) and a small reduction in cancer mortality in BCC patients (SMR 0.95, 95% CI 0.96-0.98) compared with the general population.[90] Confounding factors, such as life-style (e.g., diet habits and smoking status) and socioeconomic status, which are associated with developing NMSC and the risk of other cancers, may have affected the different study outcomes. In two large, prospective cohort studies of men and women in the United States, vitamin D intake was not related to BCC risk.[91] However, genetic studies suggest that vitamin D receptor polymorphisms may interact with nutritional vitamin D and affect the risk of NMSC and melanoma.[92-94]

The vitamin D hypothesis has raised a discussion about the benefits of UV exposure. However, 15 minutes of sun exposure on face and hands three times a week seems to be sufficient to maintain normal levels of vitamin D, suggesting that most people will spend enough time in

the sun.[95] Future studies are needed to compare vitamin D levels in patients with NMSC and those without NMSC, and to further explain the observed differences.

Health related quality of life and depression in dermatology

In general, psychodermatologic disorders are separated into psychiatric diseases that have a cutaneous association (e.g., acne exoriee and body dysmorphic disorder), and skin diseases that can be initiated or exacerbated by psychosocial stress or lead to a wide range of psychiatric disorders, including major depressive disorder, and even increased suicide risk.[96] A large group of dermatologic disorders are associated with having a major impact on HRQOL. Psychiatric disturbance and psychosocial impairment are reported in at least 30% of patients with dermatologic disorders.[97] In an Italian cross-sectional study of more than 2000 patients with a skin condition, 23% were considered to have psychiatric morbidity based on the General Health Questionnaire, and older women were especially at risk.[98] The impact of a disease on patients' lives did not correlate well with disease severity, and physicians are likely to underestimate the impact of the disease. The domains affected by dermatologic conditions differ between skin diseases. Inflammatory dermatoses have a larger impact on functional and physical domains, whereas vitiligo and alopecia areata may have a large effect on emotional well-being, and skin cancer affects anxiety and fear of recurrence.[99] These differences between diseases emphasize the need for selecting the most optimal HRQOL instruments for study goals and populations.[99]

In dermatology, the impact of psoriasis is probably the most studied. HRQOL impairment, assessed by the "SF-36 Health Survey", in patients with psoriasis is comparable to that of patients with chronic diseases such as cancer, arthritis, heart disease, and diabetes.[100] Compared with the general population, the prevalence of depression was significantly higher in patients with psoriasis.[101-103] A cross-sectional survey (response rate of 61%) noted depressive symptoms among 60% of the 2391 individuals with psoriasis. Lower educational levels, younger age, and the presence of itch were associated with reporting more depressive symptoms.[102, 104, 105] Data on the exact prevalence of depression among patients with psoriasis are not available, since different depression scoring methods or self reported data were used in the various studies on this association. Higher levels of anxiety and depressive symptoms have also been reported in patients with atopic dermatitis, which may represent an underlying primary depressive disorder in some patients who have atopic dermatitis.[106-108] Consistent with findings in patients with psoriasis, the pruritus severity was also directly related to the presence of depressive symptoms among patients with atopic dermatitis.[109] A recent study suggested that the activation of the TNF-alpha system may contribute to the development of a depressive disorder. This hypothesis was based on an examination of the disease history of more than 1000 patients suffering from acute depressive episodes, where a history of depression was associated with a higher

incidence of atopic eczema.[110] In patients with acute depression, the TNF-alpha levels and their soluble plasma receptor levels were also significantly elevated, suggesting a role for TNFalpha in this association. In psoriasis, treatment with a TNF-alpha antagonist affected the presence of depression, which may have been related to a patients' decreased inflammatory state or improved HRQOL due to disease control.[111]

Physicians treating patients with a dermatologic disease should be alert to the impact of the disease on patients' lives, which may results in decreased HRQOL, feelings of stigmatization, or depressions. In conjunction to dermatologic care, psychological counseling or psychotropic medication may optimize the management of a subgroup of patients with chronic skin diseases. Moreover, a more holistic approach is likely to reduce the physical and emotional burden for patients, and increase satisfaction with care and treatment compliance.

References

1. Feinstein A. The pretherapeutic classification of comorbidity in chronic disease. J Chron Dis 1970;23:455-568.
2. Wikipedia. Comorbidity. Available at: http://en.wikipedia.org/wiki/Comorbidity. Last Accessed 29 september, 2008.
3. Chen T, Bertenthal D, Sahay A, Sen S, Chren MM. Predictors of skin-related quality of life after treatment of cutaneous basal cell carcinoma and squamous cell carcinoma. Arch Dermatol 2007;143(11):1386-92.
4. Christophers E. Comorbidities in psoriasis. Clin Dermatol 2007;25(6):529-34.
5. Gelfand JM, Gladman DD, Mease PJ, et al. Epidemiology of psoriatic arthritis in the population of the United States. J Am Acad Dermatol 2005;53(4):573-7.
6. Moll JM, Wright V. Psoriatic arthritis. Semin Arthritis Rheum 1973;3(1):55-78.
7. Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum 2006;54(8):2665-73.
8. Finzi AF, Gibelli E. Psoriatic arthritis. Int J Dermatol 1991;30(1):1-7.
9. Rahman P, Gladman DD, Cook RJ, Zhou Y, Young G, Salonen D. Radiological assessment in psoriatic arthritis. Br J Rheumatol 1998;37(7):760-5.
10. Gladman DD, Mease PJ, Ritchlin CT, et al. Adalimumab for long-term treatment of psoriatic arthritis: forty-eight week data from the adalimumab effectiveness in psoriatic arthritis trial. Arthritis Rheum 2007;56(2):476-88.
11. Kavanaugh AF, Ritchlin CT. Systematic review of treatments for psoriatic arthritis: an evidence based approach and basis for treatment guidelines. J Rheumatol 2006;33(7):1417-21.
12. Krueger G, Ellis CN. Psoriasis--recent advances in understanding its pathogenesis and treatment. J Am Acad Dermatol 2005;53(1 Suppl 1):S94-100.
13. Wakkee M, Thio HB, Prens EP, Sijbrands EJ, Neumann HA. Unfavorable cardiovascular risk profiles in untreated and treated psoriasis patients. Atherosclerosis 2007;190(1):1-9.
14. McDonald CJ, Calabresi P. Occlusive vascular disease in psoriatic patients. N Engl J Med 1973;288(17):912.
15. Lindegard B. Diseases associated with psoriasis in a general population of 159,200 middle-aged, urban, native Swedes. Dermatologica 1986;172(6):298-304.
16. Stern RS, Lange R. Cardiovascular disease, cancer, and cause of death in patients with psoriasis: 10 years prospective experience in a cohort of 1,380 patients. J Invest Dermatol 1988;91(3):197-201.
17. Mallbris L, Akre O, Granath F, et al. Increased risk for cardiovascular mortality in psoriasis inpatients but not in outpatients. Eur J Epidemiol 2004;19(3):225-30.
18. Sommer DM, Jenisch S, Suchan M, Christophers E, Weichenthal M. Increased prevalence of the metabolic syndrome in patients with moderate to severe psoriasis. Arch Dermatol Res 2006;298(7):321-8.
19. Gisondi P, Tessari G, Conti A, et al. Prevalence of metabolic syndrome in patients a hospital-based case-control study. Br J Dermatol 2007;157(1):68-73.
20. Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB. Risk of myocardial infarction in patients with psoriasis. Jama 2006;296(14):1735-41.
21. Kaye JA, Li L, Jick SS. Incidence of risk factors for myocardial infarction and other vascular diseases in patients with psoriasis. Br J Dermatol 2008.
22. Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB, Gelfand JM. Prevalence of cardiovascular risk factors in patients with psoriasis. J Am Acad Dermatol 2006;55(5):829-35.

23. Setty AR, Curhan G, Choi HK. Obesity, waist circumference, weight change, and the risk of psoriasis in women: Nurses' Health Study II. Arch Intern Med 2007;167(15):1670-5.
24. Naldi L, Chatenoud L, Linder D, et al. Cigarette smoking, body mass index, and stressful life events as risk factors for psoriasis: results from an Italian case-control study. J Invest Dermatol 2005;125(1):61-7.
25. Brauchli YB, Jick SS, Curtin F, Meier CR. Association between beta-blockers, other antihypertensive drugs and psoriasis: population-based case-control study. Br J Dermatol 2008;158(6):1299-307.
26. Wakkee M, van der Linden M, Nijsten T. Psoriasis appears not to be directly related with using cardiovascular and antidiabetic drugs. J Invest Dermatol 2008;128:2548.
27. Kimball AB, Gladman D, Gelfand JM, et al. National Psoriasis Foundation clinical consensus on psoriasis comorbidities and recommendations for screening. J Am Acad Dermatol 2008;58(6):1031-42.
28. Margolis D, Bilker W, Hennessy S, Vittorio C, Santanna J, Strom BL. The risk of malignancy associated with psoriasis. Arch Dermatol 2001;137(6):778-83.
29. Frentz G, Olsen JH. Malignant tumours and psoriasis: a follow-up study. Br J Dermatol 1999;140(2):237-42.
30. Boffetta P, Gridley G, Lindelof B. Cancer risk in a population-based cohort of patients hospitalized for psoriasis in Sweden. J Invest Dermatol 2001;117(6):1531-7.
31. Marcil I, Stern RS. Squamous-cell cancer of the skin in patients given PUVA and ciclosporin: nested cohort crossover study. Lancet 2001;358(9287):1042-5.
32. Stern RS. The risk of melanoma in association with long-term exposure to PUVA. J Am Acad Dermatol 2001;44(5):755-61.
33. Roelofzen JH, Aben KK, van der Valk PG, van Houtum JL, van de Kerkhof PC, Kiemeney LA. Coal tar in dermatology. J Dermatolog Treat 2007;18(6):329-34.
34. Naldi L, Parazzini F, Brevi A, et al. Family history, smoking habits, alcohol consumption and risk of psoriasis. Br J Dermatol 1992;127(3):212-7.
35. Poikolainen K, Reunala T, Karvonen J, Lauharanta J, Karkkainen P. Alcohol intake: a risk factor for psoriasis in young and middle aged men? Bmj 1990;300(6727):780-3.
36. Gelfand JM, Berlin J, Van Voorhees A, Margolis DJ. Lymphoma rates are low but increased in patients with psoriasis: results from a population-based cohort study in the United Kingdom. Arch Dermatol 2003;139(11):1425-9.
37. Gelfand JM, Shin DB, Neimann AL, Wang X, Margolis DJ, Troxel AB. The risk of lymphoma in patients with psoriasis. J Invest Dermatol 2006;126(10):2194-201.
38. Stern RS. Lymphoma risk in psoriasis: results of the PUVA follow-up study. Arch Dermatol 2006;142(9):1132-5.
39. Paul CF, Ho VC, McGeown C, et al. Risk of malignancies in psoriasis patients treated with cyclosporine: a 5 y cohort study. J Invest Dermatol 2003;120(2):211-6.
40. Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. Jama 2006;295(19):2275-85.
41. Norrlind R. The significance of infections in the origination of psoriasis. Acta Rheumatol Scand 1955;1(2):135-44.
42. Gudjonsson JE, Thorarinsson AM, Sigurgeirsson B, Kristinsson KG, Valdimarsson H. Streptococcal throat infections and exacerbation of chronic plaque psoriasis: a prospective study. Br J Dermatol 2003;149(3):530-4.
43. Tomi NS, Kranke B, Aberer E. Staphylococcal toxins in patients with psoriasis, atopic dermatitis, and erythroderma, and in healthy control subjects. J Am Acad Dermatol 2005;53(1):67-72.
44. Henseler T, Christophers E. Disease concomitance in psoriasis. J Am Acad Dermatol 1995;32(6):982-6.

45. Harder J, Bartels J, Christophers E, Schroder JM. A peptide antibiotic from human skin. Nature 1997;387(6636):861.
46. Lande R, Gregorio J, Facchinetti V, et al. Plasmacytoid dendritic cells sense self-DNA coupled with antimicrobial peptide. Nature 2007;449(7162):564-9.
47. Hollox EJ, Huffmeier U, Zeeuwen PL, et al. Psoriasis is associated with increased beta-defensin genomic copy number. Nat Genet 2008;40(1):23-5.
48. Drancourt M, Argenson JN, Tissot Dupont H, Aubaniac JM, Raoult D. Psoriasis is a risk factor for hip-prosthesis infection. Eur J Epidemiol 1997;13(2):205-7.
49. Sadick NS, McNutt NS, Kaplan MH. Papulosquamous dermatoses of AIDS. J Am Acad Dermatol 1990;22(6 Pt 2):1270-7.
50. Patel RV, Weinberg JM. Psoriasis in the patient with human immunodeficiency virus, part 1: review of pathogenesis. Cutis 2008;82(2):117-22.
51. Zhang XJ, Zhang AP, Yang S, et al. Association of HLA class I alleles with psoriasis vulgaris in southeastern Chinese Hans. J Dermatol Sci 2003;33(1):1-6.
52. Goh BK, Chan RK, Sen P, et al. Spectrum of skin disorders in human immunodeficiency virus-infected patients in Singapore and the relationship to CD4 lymphocyte counts. Int J Dermatol 2007;46(7):695-9.
53. Smith JD, Knox JM. Psoriasis, methotrexate and tuberculosis. Br J Dermatol 1971;84(6):590-3.
54. Vachharajani TJ, Oza UG, Phadke AG, Kirpalani AL. Tuberculosis in renal transplant recipients: rifampicin sparing treatment protocol. Int Urol Nephrol 2002;34(4):551-3.
55. Kroesen S, Widmer AF, Tyndall A, Hasler P. Serious bacterial infections in patients with rheumatoid arthritis under anti-TNF-alpha therapy. Rheumatology (Oxford) 2003;42(5):617-21.
56. Lebwohl M, Bagel J, Gelfand JM, et al. From the Medical Board of the National Psoriasis Foundation: monitoring and vaccinations in patients treated with biologics for psoriasis. J Am Acad Dermatol 2008;58(1):94-105.
57. Lee FI, Bellary SV, Francis C. Increased occurrence of psoriasis in patients with Crohn's disease and their relatives. Am J Gastroenterol 1990;85(8):962-3.
58. Kia KF, Nair RP, Ike RW, Hiremagalore R, Elder JT, Ellis CN. Prevalence of antigliadin antibodies in patients with psoriasis is not elevated compared with controls. Am J Clin Dermatol 2007;8(5):301-5.
59. Michaelsson G, Gerden B, Ottosson M, et al. Patients with psoriasis often have increased serum levels of IgA antibodies to gliadin. Br J Dermatol 1993;129(6):667-73.
60. Damasiewicz-Bodzek A, Wielkoszynski T. Serologic markers of celiac disease in psoriatic patients. J Eur Acad Dermatol Venereol 2008.
61. Dreiher J, Weitzman D, Shapiro J, Davidovici B, Cohen AD. Psoriasis and chronic obstructive pulmonary disease: a case-control study. Br J Dermatol 2008.
62. Spergel JM, Paller AS. Atopic dermatitis and the atopic march. J Allergy Clin Immunol 2003;112(6 Suppl):S118-27.
63. Burrows B, Martinez FD, Halonen M, Barbee RA, Cline MG. Association of asthma with serum IgE levels and skin-test reactivity to allergens. N Engl J Med 1989;320(5):271-7.
64. Wuthrich B. Serum IgE in atopic dermatitis: relationship to severity of cutaneous involvement and course of disease as well as coexistence of atopic respiratory diseases. Clin Allergy 1978;8(3):241-8.
65. Eichenfield LF, Hanifin JM, Beck LA, et al. Atopic dermatitis and asthma: parallels in the evolution of treatment. Pediatrics 2003;111(3):608-16.
66. Kondo H, Ichikawa Y, Imokawa G. Percutaneous sensitization with allergens through barrier-disrupted skin elicits a Th2-dominant cytokine response. Eur J Immunol 1998;28(3):769-79.

67. Warner JO. A double-blinded, randomized, placebo-controlled trial of cetirizine in preventing the onset of asthma in children with atopic dermatitis: 18 months' treatment and 18 months' posttreatment follow-up. J Allergy Clin Immunol 2001;108(6):929-37.
68. Bustos GJ, Bustos D, Bustos GJ, Romero O. Prevention of asthma with ketotifen in preasthmatic children: a three-year follow-up study. Clin Exp Allergy 1995;25(6):568-73.
69. Cole GW, Silverberg NL. The adherence of Staphylococcus aureus to human corneocytes. Arch Dermatol 1986;122(2):166-9.
70. Ong PY, Ohtake T, Brandt C, et al. Endogenous antimicrobial peptides and skin infections in atopic dermatitis. N Engl J Med 2002;347(15):1151-60.
71. Zeeuwen PL, de Jongh GJ, Rodijk-Olthuis D, et al. Genetically programmed differences in epidermal host defense between psoriasis and atopic dermatitis patients. PLoS ONE 2008;3(6):e2301.
72. Birnie AJ, Bath-Hextall F, Ravenscroft JC, Williams HC. Interventions to reduce Staphylococcus aureus in the management of atopic eczema. J Invest Dermatol 2008;128(2557).
73. Lin YT, Wang CT, Chiang BL. Role of bacterial pathogens in atopic dermatitis. Clin Rev Allergy Immunol 2007;33(3):167-77.
74. Wollenberg A, Klein E. Current aspects of innate and adaptive immunity in atopic dermatitis. Clin Rev Allergy Immunol 2007;33(1-2):35-44.
75. Yoon M, Spear PG. Disruption of adherens junctions liberates nectin-1 to serve as receptor for herpes simplex virus and pseudorabies virus entry. J Virol 2002;76(14):7203-8.
76. Linos E, Raine T, Alonso A, Michaud D. Atopy and risk of brain tumors: a meta-analysis. J Natl Cancer Inst 2007;99(20):1544-50.
77. Wen W, Shu XO, Linet MS, et al. Allergic disorders and the risk of childhood acute lymphoblastic leukemia (United States). Cancer Causes Control 2000;11(4):303-7.
78. Spector L, Groves F, DeStefano F, et al. Medically recorded allergies and the risk of childhood acute lymphoblastic leukaemia. Eur J Cancer 2004;40(4):579-84.
79. Schuz J, Morgan G, Bohler E, Kaatsch P, Michaelis J. Atopic disease and childhood acute lymphoblastic leukemia. Int J Cancer 2003;105(2):255-60.
80. Wang H, Diepgen TL. Is atopy a protective or a risk factor for cancer? A review of epidemiological studies. Allergy 2005;60(9):1098-111.
81. Alkhateeb A, Fain PR, Thody A, Bennett DC, Spritz RA. Epidemiology of vitiligo and associated autoimmune diseases in Caucasian probands and their families. Pigment Cell Res 2003;16(3):208-14.
82. Shong YK, Kim JA. Vitiligo in autoimmune thyroid disease. Thyroidology 1991;3(2):89-91.
83. Schallreuter KU, Lemke R, Brandt O, et al. Vitiligo and other diseases: coexistence or true association? Hamburg study on 321 patients. Dermatology 1994;188(4):269-75.
84. Amerio P, Tracanna M, De Remigis P, et al. Vitiligo associated with other autoimmune diseases: polyglandular autoimmune syndrome types 3B+C and 4. Clin Exp Dermatol 2006;31(5):746-9.
85. Dittmar M, Kahaly GJ. Polyglandular autoimmune syndromes: immunogenetics and long-term follow-up. J Clin Endocrinol Metab 2003;88(7):2983-92.
86. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. Arch Intern Med 2000;160(4):526-34.
87. Hollowell JG, Staehling NW, Flanders WD, et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab 2002;87(2):489-99.
88. Jin Y, Mailloux CM, Gowan K, et al. NALP1 in vitiligo-associated multiple autoimmune disease. N Engl J Med 2007;356(12):1216-25.

89. Soerjomataram I, Louwman WJ, Lemmens VE, Coebergh JW, de Vries E. Are patients with skin cancer at lower risk of developing colorectal or breast cancer? Am J Epidemiol 2008;167(12):1421-9.
90. Jensen AO, Bautz A, Olesen AB, Karagas MR, Sorensen HT, Friis S. Mortality in Danish patients with nonmelanoma skin cancer, 1978-2001. Br J Dermatol 2008;159(2):419-25.
91. Hunter DJ, Colditz GA, Stampfer MJ, Rosner B, Willett WC, Speizer FE. Diet and risk of basal cell carcinoma of the skin in a prospective cohort of women. Ann Epidemiol 1992;2(3):231-9.
92. Han J, Colditz GA, Hunter DJ. Polymorphisms in the MTHFR and VDR genes and skin cancer risk. Carcinogenesis 2007;28(2):390-7.
93. Li C, Liu Z, Zhang Z, et al. Genetic variants of the vitamin D receptor gene alter risk of cutaneous melanoma. J Invest Dermatol 2007;127(2):276-80.
94. Bikle DD. Vitamin D receptor, UVR, and skin cancer: a potential protective mechanism. J Invest Dermatol 2008;128(10):2357-61.
95. Holick MF. McCollum Award Lecture, 1994: vitamin D--new horizons for the 21st century. Am J Clin Nutr 1994;60(4):619-30.
96. Cotterill JA, Cunliffe WJ. Suicide in dermatological patients. Br J Dermatol 1997;137(2):246-50.
97. Fried RG, Gupta MA, Gupta AK. Depression and skin disease. Dermatol Clin 2005;23(4):657-64.
98. Sampogna F, Picardi A, Chren MM, et al. Association between poorer quality of life and psychiatric morbidity in patients with different dermatological conditions. Psychosom Med 2004;66(4):620-4.
99. Both H, Essink-Bot ML, Busschbach J, Nijsten T. Critical review of generic and dermatology-specific health-related quality of life instruments. J Invest Dermatol 2007;127(12):2726-39.
100. Rapp SR, Feldman SR, Exum ML, Fleischer AB, Jr., Reboussin DM. Psoriasis causes as much disability as other major medical diseases. J Am Acad Dermatol 1999;41(3 Pt 1):401-7.
101. Sharma N, Koranne RV, Singh RK. Psychiatric morbidity in psoriasis and vitiligo: a comparative study. J Dermatol 2001;28(8):419-23.
102. Esposito M, Saraceno R, Giunta A, Maccarone M, Chimenti S. An Italian study on psoriasis and depression. Dermatology 2006;212(2):123-7.
103. Akay A, Pekcanlar A, Bozdag KE, Altintas L, Karaman A. Assessment of depression in subjects with psoriasis vulgaris and lichen planus. J Eur Acad Dermatol Venereol 2002;16(4):347-52.
104. Gupta MA, Gupta AK, Watteel GN. Early onset (< 40 years age) psoriasis is comorbid with greater psychopathology than late onset psoriasis: a study of 137 patients. Acta Derm Venereol 1996;76(6):464-6.
105. Gupta MA, Gupta AK, Kirkby S, et al. Pruritus in psoriasis. A prospective study of some psychiatric and dermatologic correlates. Arch Dermatol 1988;124(7):1052-7.
106. Ahmar H, Kurban AK. Psychological profile of patients with atopic dermatitis. Br J Dermatol 1976;95(4):373-7.
107. Linnet J, Jemec GB. An assessment of anxiety and dermatology life quality in patients with atopic dermatitis. Br J Dermatol 1999;140(2):268-72.
108. Hashiro M, Okumura M. Anxiety, depression and psychosomatic symptoms in patients with atopic dermatitis: comparison with normal controls and among groups of different degrees of severity. J Dermatol Sci 1997;14(1):63-7.
109. Gupta MA, Gupta AK, Schork NJ, Ellis CN. Depression modulates pruritus perception: a study of pruritus in psoriasis, atopic dermatitis, and chronic idiopathic urticaria. Psychosom Med 1994;56(1):36-40.
110. Himmerich H, Fulda S, Linseisen J, et al. Depression, comorbidities and the TNF-alpha system. Eur Psychiatry 2008.
111. Tyring S, Gottlieb A, Papp K, et al. Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. Lancet 2006;367(9504):29-35.

Chapter 3

Unfavorable cardiovascular risk profiles in untreated and treated psoriasis patients

M. Wakkee
H.B. Thio
E.P. Prens
E.J.G. Sijbrands
H.A.M. Neumann

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Abstract

Psoriasis is a chronic inflammatory skin disease that is associated with an increased cardiovascular risk profile. The systemic inflammation present in psoriasis, various systemic treatments for psoriasis and an increased prevalence of unhealthy life style factors may all contribute to this unfavorable risk profile. The purpose of this article is to provide an overview of what is known about these risk factors in psoriasis, the way they influence the cardiovascular risk of psoriasis patients, and what can be done to reduce this risk. Genetic studies demonstrate that psoriasis and cardiovascular disease share common pathogenic features in which, for example inflammatory cytokines like TNF-alpha and IL-1 play an important role. The chronic inflammation in psoriasis has an unfavorable effect on the cardiovascular risk profile. Multiple cardiovascular risk factors seem to be influenced; the blood pressure, oxidative stress, dyslipidemia, endothelial cell dysfunction, homocysteine levels and blood platelet adhesion. Moreover, classic cardiovascular risk factors like smoking and obesity that have an increased prevalence among patients with psoriasis, indirectly also worsen the cardiovascular risk profile by stimulating the psoriasis activity. Systemic treatments in psoriasis reduce the cardiovascular risk by diminishing the inflammation, but it should be taken into account that most therapies also have adverse cardiovascular effects like dyslipidemia, hyperhomocysteinemia and hypertension. As a consequence preventive measures may be indicated at least during long-term treatments. Prospective research is warranted to accurately estimate the increased cardiovascular risk in psoriasis, to determine the underlying processes and to consider preventive measures according to the absolute risk of cardiovascular disease. The present overview provides data to advice health care providers to pay more attention to the cardiovascular risk profile in psoriasis patients.

Introduction

Psoriasis is a chronic inflammatory skin disorder affecting approximately 2% of the general population. It is characterized by epidermal hyperproliferation, abnormal differentiation of epidermal keratinocytes and a lymphocyte infiltration consisting mostly of T-lymphocytes. In the pathogenesis of psoriasis many different inflammatory cells are involved with major roles for the T-lymphocyte and the cytokine network and chemokines.[1] At the site of inflammation activated T-lymphocytes predominantly release type 1 cytokines like interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α) and interleukin-2 (IL-2). IFN-γ may contribute to hyperproliferation of keratinocytes in the skin by inhibiting their apoptosis.[2] IL-2 stimulates the T-lymphocyte proliferation and TNF-α activates and increases keratinocyte proliferation. Other effects of TNF-α are stimulation of production of cytokines from T-lymphocytes and macrophages, chemokine release from macrophages, and the expression of adhesion molecules on vascular endothelial cells. In case of such an extended inflammation, it is conceivable also to assume systemic consequences. Most health care providers, including dermatologists, do not associate psoriasis with an unfavorable cardiovascular risk profile, but more and more evidence is emerging that this might be the case. The higher prevalence of classic cardiovascular risk factors, like smoking, hypertension and obesity contribute to atherogenesis in psoriasis patients, but psoriasis itself and its systemic treatment may also stimulate premature atherogenesis, increasing the cardiovascular risk. In rheumatoid arthritis (RA), which is also a chronic inflammatory disease with a comparable pathogenesis, it has already been demonstrated that these patients have an increased prevalence of atherosclerosis compared to the general population.[3] The atherosclerosis in RA is not only associated with classic cardiovascular risk factors, but with the inflammatory process as well.[4] Additional support for this notion has come from research with laboratory mice. A mouse was created with a deficiency in the interleukin (IL)-1 receptor antagonist gene that normally functions as a naturally occurring inhibitor of IL-1.[5] These mice developed three apparently spontaneous inflammatory diseases arthritis, psoriasis-like dermatitis and arteritis.[6] This suggests that the inflammatory process in psoriasis may also affect the arterial wall, promoting the atherosclerotic process. In the present review, we describe all available evidence for the association between psoriasis and cardiovascular disease to assess the indication for risk evaluation and preventive measures in these patients.

Methods

A literature search was performed using the PubMed database. We identified 926 articles that were published in the English language from January 1970 to January 2006. The following MeSH terms were used: psoriasis, cardiovascular diseases, inflammation, atherogenesis, hydroxymethylglutaryl-coa reductase inhibitors, obesity, smoking, hypertension, homocysteine, insulin

resistance, blood platelets, oxidative stress and endothelial cells. The following text words were also searched for: cardiovascular risk, PSORS1, dyslipidemia and therapy. The identified studies were reviewed on the presence of information on the cardiovascular risk profile of psoriasis patients, resulting in a final selection of 78 studies.

Psoriasis and cardiovascular disease risk

Mallbris et al. performed a historical cohort study to assess the risk for cardiovascular mortality among psoriasis patients.[7] Remarkably, patients who were treated at least once as inpatient had a 50% increased overall risk for cardiovascular death compared to the general population. The excess risk was clearly associated with the severity of psoriasis expressed as the number of hospital admissions. Especially patients admitted at young age had an unexpectedly high excess cardiovascular mortality, whereas no increased cardiovascular mortality among outpatients with psoriasis was observed. These data suggest on the one side, that psoriasis patients with more severe disease have a substantially increased risk for cardiovascular death. On the other side, it can be argued that the available in-hospital treatment modalities contribute to this risk as well. A large 10-year prospective cohort study of psoriasis outpatients showed no increase of cardiovascular mortality compared to the general population.[8] This follow up study was performed among patients on photochemotherapy, who had an average severity of psoriasis of more than 30% affected body surface area (BSA) at entry. Unfortunately, no analysis was performed according to the affected BSA. McDonald assessed the cardiovascular morbidity by combining psoriasis data from three studies and concluded that the occurrence rate of occlusive vascular events was significantly greater in psoriatic than in the non-psoriatic dermatologic patient.[9] In this study, the percentage of body surface area affected by psoriasis appeared to influence the incidence of cardiovascular diseases particularly in the older patient. Henseler and Christophers conducted a hospital-based cross-sectional study and found an overall increase in heart failure among psoriasis inpatients.[10] Taken together, these data support the notion that an association exists between psoriasis and an unfavorable cardiovascular risk profile, especially in patients with severe psoriasis. However, differences with regard to the type of study, the selection procedures and whether or not age and the severity of psoriasis were taken into account resulted in an intricate set of combined results. For example, Wong and co-workers found that patients with psoriatic arthritis had an increased death rate of 1.3 due to cardiovascular diseases, but Shbeeb et al. did not observe a difference in lifetime survival between patients with psoriatic arthritis and the general population.[11, 12] These conflicting results may be based on the differences in disease severity. The work by Gladman et al. confirmed a selection of patients with the highest disease severity to referral centers: markers of previously active and severe disease as manifested by the prior use of medication, a high erythrocyte sedimentation rate at presentation and evidence of radiological joint damage are associated with increased mortality

in psoriatic arthritis patients.[13] Moreover, a shift from hospital based to effective outpatient care has arisen, and the present day treatment whereby the inflammatory process is modulated, may reduce the risk of subsequent cardiovascular mortality associated with psoriasis.

Psoriasis genetics and cardiovascular disease risk

Twin studies support a genetic basis of psoriasis.[14, 15] Although the way gene variants influence the disease is complex, a clear association was found with the PSORS1 gene locus on chromosome 6, accounting for approximately 35–50% of the genetic contribution to psoriasis.[16, 17] Carriers of this HLA-Cw*0602 allele exhibit an earlier disease onset, more extensive skin lesions and a more severe disease.[18] Psoriasis patients who are predisposed to have such an extended inflammation may also be at higher risk for cardiovascular complications. Since cytokines are thought to play a pivotal role in psoriasis, the genes that encode them are also potential candidate genetic markers for disease susceptibility and severity, as well as cardiovascular disease risk. For example, IL-1 receptor antagonist-deficient mice that develop both psoriasis and arteritis, fit well with the reported dysregulation of the IL-1 family of cytokines in psoriasis.[6, 19] Furthermore, TNF-α is overexpressed in lesional skin, in the circulation of patients with psoriasis, as well as in failing myocardium.[20, 21] Studies on transgenic mice that overexpress TNF-α specifically in the heart, showed that they develop myocardial inflammation and subsequent heart failure.[22] Another interesting association has been demonstrated between the apolipoproteine (apo) E4 allele and chronic plaque psoriasis and guttate psoriasis, suggesting a possible pathogenic role of ApoE in psoriasis.[23] Apo E is also involved as a ligand in the clearance of triglyceride-rich lipoproteins from the circulation. Individuals with the ApoE4 isoform tend to have increased total cholesterol, low-density lipoprotein (LDL) cholesterol and apolipoprotein B, and a high prevalence of heart disease.[24] The underlying mechanism is not fully understood and possibly involves downregulation of LDL receptors.

Psoriasis treatment and cardiovascular disease risk

Depending on the severity of the psoriasis various treatments are available. Anti-psoriatic therapies are mainly targeted at reducing the inflammatory process in the skin. Topical treatments, corticosteroids, Vitamin D analogues, dithranol and tar are preferred in mild forms of psoriasis (<10% of the body area affected). The next option will be phototherapy, which can be divided into UVB-light therapy and photochemotherapy (PUVA). In more severe forms of psoriasis (>10% of the body area affected) systemic therapy is used. We will shortly discuss the available systemic therapies and their adverse systemic effects with special focus on cardiovascular effects.

Methotrexate (MTX) is a frequently prescribed agent. MTX blocks DNA synthesis in; rapidly proliferating epidermal cells, T- and B-lymphocytes and disrupts cytokine secretion.[25] Hepatotoxicity is a well-known adverse effect of MTX. After a cumulative dose of 1.5 g a liver biopsy is recommended to examine if there are hepatotoxic effects. MTX also reduces plasma and red blood cell folate levels via reduced activity of dihydrofolate reductase, which subsequently increases homocysteine levels.[26] Therefore folic acid is usually added to methotrexate to reduce its toxicity and its effect on homocysteine levels.[27]

The immunosuppressive drug cyclosporin inhibits T-cell activation and the transcription of IL-2 and other cytokines important in the pathogenesis of psoriasis.[28] Cyclosporin is associated with renal toxicity that is related to the dose and the duration of treatment.[29] Other side effects of cyclosporin are metabolic abnormalities like hypertriglyceridemia and hypercholesterolemia.

Acitretin is an oral retinoid that by binding to retinoic acid receptors alters the transcription of genes coding for proteins involved in the pathogenesis of psoriasis, especially in keratinocytes. The most common side effects are dose-dependent and are mucocutaneous adverse effects such as cheilitis and hair loss, requiring dose reduction in some patients. Hepatotoxicity and hypercholesterolemia, triglyceridemia and low high-density lipoprotein (HDL) cholesterol are also side effects of acitretin.[30]

Oral fumaric acid ester therapy is another systemic treatment for psoriasis in Western Europe. Fumaric acid esters promote the secretion of type 2 cytokines (IL-4, IL-5 and IL-10) that may inhibit type 1 cytokines. The cytokine switch appears to be beneficial in psoriasis.[31] Gastrointestinal complaints and flushing are often reported and frequently a relative lymphocytopenia occurs.[32] No significant changes in cholesterol levels have been noticed with the use of fumaric acid esters.[33]

Biological response modifiers are protein molecules constructed to specifically target a particular molecule on cells or a cytokine involved in the pathogenesis of psoriasis. At this moment they can be classified into T-cell modifying agents and TNF-α inhibitors. Primary concerns with the use of biologicals are increased risk of infection and relative uncertainty about the long-term adverse effects and safety. The effect of TNF-α inhibitors on serum HDL levels has been investigated in patients with rheumatoid arthritis. On the first day it decreases HDL, but most likely it favorably increases HDL during prolonged treatment.[34, 35] Irace et al. also observed a transitory improvement in endothelial function after anti-TNF-α treatment.[35]

In summary, the iatrogenic effects of systemic psoriasis therapies might also enhance the cardiovascular risk profile: the increased homocysteine level after MTX use, the dyslipidemic changes related to the use of cyclosporin and acitretin, but also a potential beneficial increase of HDL occurs when using TNF-α inhibitors.

Classic cardiovascular risk factors in psoriasis

Lipid profile

In moderate to severe psoriasis, a significantly deteriorated lipid profile was observed compared to healthy controls with higher values of cholesterol, triglycerides, LDL and low HDL.[36] In less severe cases, only values of HDL were significantly lower compared to controls.[37] Moreover, the lipid profile may be affected during systemic treatment with anti-psoriatic medication like acitretin or cyclosporin, potentially increasing the overall risk for cardiovascular diseases.

Hypertension

In a hospital-based study, Lindegard and co-workers observed that psoriasis was significantly associated with hypertension and also Henseler and Christophers found it twice as frequent in psoriasis as in control subjects.[10, 38] Inerot et al. reported no increased frequency of hypertension in a population of patients with psoriasis sampled from a patient organization.[39] A probable explanation for this difference is that in the latter study patients had a mild form of psoriasis, which was also suggested by the authors, while Henseler and Christophers described that the majority of their psoriasis patients were hospitalized at first diagnosis. Another explanation might be the relatively low mean age of approximately 40 in the study of Inerot et al.

Factors contributing to the association between psoriasis and hypertension may be the production of endothelin-1, the inflammatory process itself and the adverse effects of cyclosporin treatment. Endothelin-1 is a peptide produced by keratinocytes as an autocrine growth factor for these cells. Bonifati et al. reported that endothelin-1 was increased in both the sera and lesional skin of patients with psoriasis compared to normal subjects and the values also correlated with the psoriasis severity.[40] Endothelin-1 has very potent systemic vasoconstricting properties and may therefore have systemic effects and contribute to elevated blood pressure in psoriasis patients. If the inflammatory process in psoriasis influences the blood pressure has not been investigated yet, although other work does provides circumstantial evidence. Like oxidative stress, also present in mild psoriasis, has been implicated to play a role in hypertension by the nitric oxide (NO) destructive effects of reactive oxygen species (ROS), which impair the endothelium dependent vasodilatation.[41] The third contributing factor is the frequent prescription of cyclosporin that is known for its hypertensive side effect, especially in long-term maintenance therapy.[42]

Obesity

In a case-control study, Naldi et al. showed that psoriasis of recent onset was positively correlated with body mass index (BMI), with an odds ratio of 1.6 for over weighted and 1.9 for obese patients.[43] Moreover, a Croatian study suggested that a low energy diet might be beneficial in psoriasis vulgaris treatment as a significant reduction in psoriatic skin lesions was observed after a low-energy diet.[44] Obesity is associated with a state of chronic low-grade inflammation observed by increased circulatory levels of TNF-α, C-reactive protein and IL-6 positively related to the BMI.[45, 46] Macrophages that infiltrate the adipose tissue in obesity are likely to be responsible for the production of these pro-inflammatory cytokines.[47] This pro-inflammatory state in obesity may explain the association between psoriasis and obesity. When patients with psoriasis are more likely to be obese that implies they will also have the comorbid conditions of those with obesity. The risks of diabetes, hypertension and dyslipidemia start to rise from a BMI of about 21.0 kg/m^2 thereby deteriorating the cardiovascular risk profile.[48, 49]

In both obesity as well as diabetes mellitus, TNF-α is an important mediator of insulin resistance through its ability to decrease the tyrosine kinase activity of the insulin receptor.[50] Several chronic inflammatory diseases like rheumatoid arthritis have also been associated with the presence of insulin resistance.[51] Reynoso-von Drateln et al. investigated whether this is the case in patients with psoriasis, however no differences were found in insulin secretion or sensitivity compared with control patients.[37] Nonetheless, a significant correlation was observed between the duration of psoriasis and insulin sensitivity. Henseler and Christophers, and Binazzi et al. both found an association between psoriasis and diabetes mellitus, which was probably the result of an increased prevalence of obesity in the psoriasis patients.[10, 52]

Smoking

A number of studies have examined the association between psoriasis and smoking. The most striking link has been established between smoking and pustular psoriasis.[43] Naldi et al. showed in the same paper that the risk for plaque psoriasis was also higher in current smokers and ex-smokers than in patients who had never smoked. A cross-sectional study by Herron et al., demonstrated that in their psoriasis population the prevalence of smoking was higher than in the general Utah population and higher than in the non-psoriatic patients.[53] Using questionnaires, they found that 78% smoked before the onset of psoriasis. Smoking may not only be a trigger, but it might be associated with clinical severity as well. A high intensity of smoking (>20 cigarettes daily) relative to a lower level of consumption (≤10 cigarettes daily) was associated with a more than two-fold increased risk of clinically more severe psoriasis.[54]

Recently, it has been shown that cigarette smoking induces an overproduction of IL-1β, increases the production of TNF-α and enhances the transforming of growth factor-β from mononuclear blood cells.[55] These cytokines are also raised in psoriasis and may partly explain the association with smoking.[56, 57] Nicotine also stimulates dendritic cell (DC) expression of costimulatory molecules, MHC class II and adhesion molecules.[58] This DC activation augments their capacity to stimulate the proliferation of T-lymphocytes, which also play an important role in the pathogenesis of psoriasis. Moreover, nicotine induces a significant increase in the secretion of the pro-inflammatory type 1 cytokine interleukin-12 by human DC, further contributing to the inflammatory process.

Other cardiovascular risk factors in psoriasis

Oxidative stress

Patients with psoriasis exhibit several markers of oxidative stress and show impaired antioxidant status. The oxidative stress develops when the antioxidant capacity is overwhelmed leading to oxidative damage of lipids and proteins. Oxidative stress and increased free radical generation, reactive oxygen species and superoxide anion liberation occur in inflamed skin in psoriasis.[59] Malondialdehyde (MDA), a marker of lipid peroxidation, is increased in plasma and red blood cells of patients with psoriasis. Antioxidants like β-carotene and α-tocopherol show decreased plasma levels.[60] Both function as scavengers of free radicals like lipid peroxyl radicals. The activity of glutathion peroxidase, an antioxidant enzyme is also reduced in psoriasis. This imbalance between oxidants and antioxidants is also observed in mild forms of psoriasis.[61] High levels of oxidants may favor the progression of the atherosclerotic process by promoting LDL oxidation. Oxidized LDL (Ox-LDL) is not only important for the formation of the fatty streak but it also damages the endothelium allowing continued transport of inflammatory cells and mediators into the vessel wall and all these processes generate ROS.[60] It is also clear that ROS are involved in signaling vascular smooth muscle cell migration and proliferation during the formation of atherosclerotic lesions.

Homocysteine

Hyperhomocysteinemia may constitute an independent risk factor for cardiovascular disease.[62] Homocysteine promotes many processes involved in atherosclerosis and also affects the coagulation system. Vanizor Kural et al. examined serum total homocysteine levels and its relationship with atherothrombotic markers in 30 patients with psoriasis and 30 sex and aged matched healthy volunteers.[63] The mean levels of serum total homocysteine, fibrinogen, fibronectin, soluble intercellular adhesion molecules-1, plasminogen activator inhibitor-1 (PAI-1), total cholesterol,

triglycerides and autoantibodies against oxidized LDL (AuAb-oxLDL) were increased whereas tissue plasminogen activator, Vitamin B12 and folate levels were decreased compared with healthy controls. Total homocysteine levels were negatively correlated with Vitamin B12 and positively correlated with plasminogen activator inhibitor-1 and AuAb-oxLDL. Hyperhomocysteinemia may be a risk indicator, but high levels of homocysteine change the homeostatic balance towards a prothrombotic state by increased PAI synthesis as well as by an increased fibrinogen level and stimulate atherosclerosis by the increased level of AuAb-oxLDL resulting in LDL oxidation.

Endothelial cell dysfunction

Blann suggested that one of the mechanisms of endothelial cell damage is caused by a chronic inflammatory state.[64] Chronic stimulation of the endothelial cell by cytokines may result in dysfunctional changes. Other factors like smoking, hyperinsulinemia, hypertension and hypercholesterolemia, which are often associated with psoriasis, are also deleterious to the endothelium and may accelerate endothelial cell dysfunctioning. Vascular endothelial cell dysfunction is seen as one of the early markers of atherosclerosis and is recognized as a predictor of cardiovascular events.[65] Damage to endothelium can be determined by assessing the levels of soluble endothelial cell markers, such as soluble intercellular adhesion molecule-1 (sICAM-1) and von Willebrand factor in the plasma or non-invasively by postocclusion flow-mediated vasodilatation of the brachial artery using high sensitivity brachial ultrasonography.[66-68] We propose that psoriasis might be associated with endothelial dysfunction, both because of the abundance of pro-inflammatory cytokines as well as the metabolic abnormalities found in psoriasis.

Blood platelets

Patients with psoriasis were reported to have normal platelet counts and fibrinolytic activity. Circulating platelet aggregates were not raised significantly, but a higher spontaneous platelet hyperaggregability was noticed using a platelet aggregation test.[69] This hyperaggregation of platelets is probably due to enhanced cyclooxygenase activity in these platelets.[70] It is, however, not clear whether or not this contributes to a higher risk of occlusive vascular disease. Blood platelets might contribute to the cardiovascular risk in psoriasis by another mechanism. Inflammatory signals induce the expression of proteins on the endothelial cell surface that promote the adhesion and extravasation of activated immune cells from the circulation into the underlying tissue. P-selectin and E-selectin are among the molecules expressed on the endothelial cells. Platelets also adhere to the activated human endothelial cell monolayer by attaching to the selectins.[71] Thereafter, platelets firmly adhere to the vascular endothelium via β3 integrins, release other pro-inflammatory substances and induce a proatherogenic phenotype of ECs. Subsequently, they recruit circulating leukocytes, bind them and activate them, thereby initiating leukocyte transmigration and foam cell formation. Thus, platelets provide the

inflammatory cellular basis for plaque formation and may contribute to the early processes of atherosclerosis in psoriasis.[71]

Possible role of statins in psoriasis

HMG-CoA reductase inhibitors (statins) have pleiotropic effects and may be beneficial to patients with psoriasis: in addition to cholesterol lowering, statins have other anti-atherosclerotic, cardiovascular risk reducing effects.[72] Statins directly upregulate endothelial nitric oxide synthase in vitro, which reduces the monocyte adhesion to the endothelial surface and the oxidation of LDL. Moreover, statins also have immunomodulatory activities that may improve the psoriasis skin.[73] By binding to HMG-CoA reductase statins inhibit the cholesterol biosynthesis and reduce isoprenoid levels in the mevalonate pathway. Especially mevalonate is an important substrate in cholesterol biosynthesis that activates inflammation via intracellular signal transduction systems.[74] In this way statins may cause a shift from pro-inflammatory to anti-inflammatory conditions in psoriasis patients that might be beneficial to the skin disorder as well as the cardiovascular risk profile.[75, 76] These observations suggest a potential role for statins in psoriasis patients.

Discussion

It is clear that psoriasis is associated with a higher risk of cardiovascular disease. The excess risk is influenced by the psoriasis severity, indicating an inflammation dependent effect. This association is corroborated by genetic studies confirming overlapping pathogenic features, like overexpression of pro-inflammatory cytokines in both psoriasis and cardiovascular disease. It would be interesting to be able to confirm the association of PSORS1 with cardiovascular disease in future research.

If systemic inflammation promotes atherosclerosis, then it follows that the use of anti-inflammatory agents in psoriasis may decrease the cardiovascular disease burden in this population. Unfortunately most of these drugs also have adverse effects on the cardiovascular risk profile, resulting in a more ambivalent effect. Methotrexate treatment in RA has proven to offer substantial protection against cardiovascular disease, far outweighing the potential effect of hyperhomocysteinemia.[77] The resultant of other therapies has not been investigated yet, but we assume that side effects like hypertension or dyslipidemia will dramatically reduce the advantageous anti-inflammatory effects.

As discussed in detail, the systemic inflammation in psoriasis acts on many different cardiovascular risk factors; hypertension, oxidative stress, dyslipidemia, endothelial cell dysfunction,

homocysteine levels and blood platelet adhesion. Although for some cardiovascular risk factors the association with psoriasis is more robust than others, there is unquestionably a considerable impact of this systemic inflammation on the cardiovascular risk profile. The presence of unhealthy life style factors like smoking and obesity are associated with psoriasis onset and severity by creating a pro-inflammatory environment. These classic cardiovascular risk factors affect the process of atherosclerosis directly, but in the same way also indirectly by stimulating the psoriasis activity.

Conclusion

Psoriasis is associated with an unfavorable cardiovascular risk profile: many clinical studies confirm this association. The cardiovascular risk factors are accumulating in psoriasis patients. Three elements contribute to the cardiovascular risk profile in psoriasis patients (Fig. 1). The most important one is the systemic inflammation in psoriasis; this deteriorates the complete cardiovascular risk profile. Secondly, systemic therapies of which its effect depends on the sum of anti-inflammatory effects and atherogenic side effects. Finally, life style factors like smoking and obesity, that add to the cardiovascular risk profile directly as a classic cardiovascular risk factor, and also indirectly by increasing the psoriasis activity. The assemblage of risk factors seems to increase the risk of cardiovascular disease, which is supported by a number

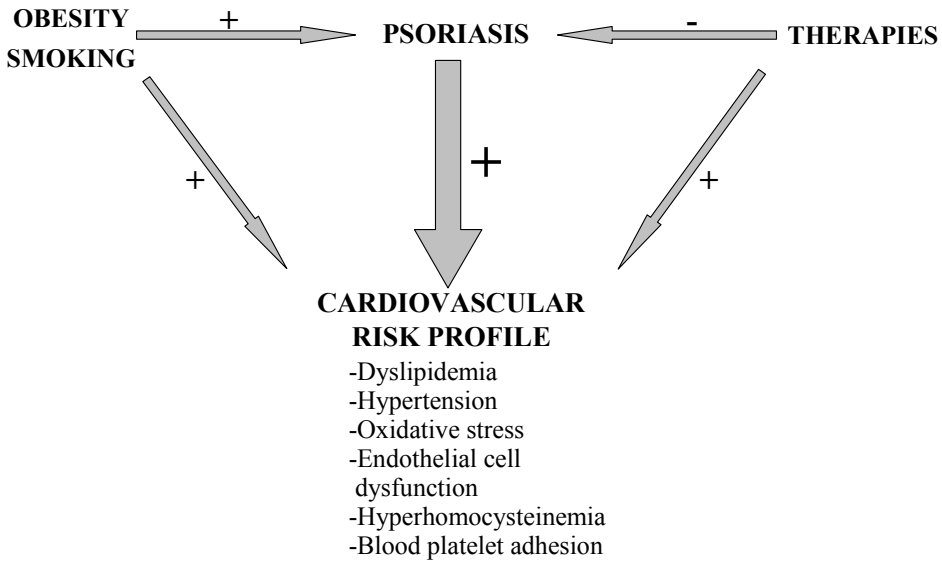

Figure 1. Psoriasis represents a state of systemic inflammation with subsequent unfavourable effects on the cardiovascular risk profile. The increased prevalence of unhealthy life style factors like smoking and obesity influence the cardiovascular risk profile directly and also indirectly by stimulating the psoriasis severity. Anti-psoriatic therapies have a more bivalent effect, they reduce the chronic inflammation, but cardiovascular side-effects may reduce this beneficial effect.

of epidemiological studies. The future impact of an unfavorable cardiovascular risk profile in psoriasis can be of great importance, not only for the care of patients with psoriasis, but also in the research field of psoriasis. Based on the carefully collected evidence, we propose to estimate the absolute risk of cardiovascular disease in psoriasis patients, to take this into account when choosing a psoriasis treatment and to treat them when necessary according to the international consensus statement on prevention of cardiovascular disease in which statins may play a key role.[78] Further study may identify targets that enable simultaneous intervention for psoriasis and cardiovascular risk.

References

1. Krueger G, Ellis CN. Psoriasis--recent advances in understanding its pathogenesis and treatment. Journal of the American Academy of Dermatology 2005;53(1 Suppl 1):S94-100.
2. Chaturvedi V, Qin JZ, Denning MF, Choubey D, Diaz MO, Nickoloff BJ. Apoptosis in proliferating, senescent, and immortalized keratinocytes. The Journal of biological chemistry 1999;274(33):23358-67.
3. Roman MJ, Moeller E, Davis A, et al. Preclinical carotid atherosclerosis in patients with rheumatoid arthritis. Annals of internal medicine 2006;144(4):249-56.
4. Dessein PH, Joffe BI, Veller MG, et al. Traditional and nontraditional cardiovascular risk factors are associated with atherosclerosis in rheumatoid arthritis. The Journal of rheumatology 2005;32(3):435-42.
5. Horai R, Saijo S, Tanioka H, et al. Development of chronic inflammatory arthropathy resembling rheumatoid arthritis in interleukin 1 receptor antagonist-deficient mice. The Journal of experimental medicine 2000;191(2):313-20.
6. Shepherd J, Little MC, Nicklin MJ. Psoriasis-like cutaneous inflammation in mice lacking interleukin-1 receptor antagonist. The Journal of investigative dermatology 2004;122(3):665-9.
7. Mallbris L, Akre O, Granath F, et al. Increased risk for cardiovascular mortality in psoriasis inpatients but not in outpatients. European journal of epidemiology 2004;19(3):225-30.
8. Stern RS, Lange R. Cardiovascular disease, cancer, and cause of death in patients with psoriasis: 10 years prospective experience in a cohort of 1,380 patients. The Journal of investigative dermatology 1988;91(3):197-201.
9. McDonald CJ. Cardiovascular disease in psoriasis. The Journal of investigative dermatology 1989;92(4):646-7.
10. Henseler T, Christophers E. Disease concomitance in psoriasis. Journal of the American Academy of Dermatology 1995;32(6):982-6.
11. Wong K, Gladman DD, Husted J, Long JA, Farewell VT. Mortality studies in psoriatic arthritis: results from a single outpatient clinic. I. Causes and risk of death. Arthritis and rheumatism 1997;40(10):1868-72.
12. Shbeeb M, Uramoto KM, Gibson LE, O'Fallon WM, Gabriel SE. The epidemiology of psoriatic arthritis in Olmsted County, Minnesota, USA, 1982-1991. The Journal of rheumatology 2000;27(5):1247-50.
13. Gladman DD, Farewell VT, Wong K, Husted J. Mortality studies in psoriatic arthritis: results from a single outpatient center. II. Prognostic indicators for death. Arthritis and rheumatism 1998;41(6):1103-10.
14. Brandrup F, Holm N, Grunnet N, Henningsen K, Hansen HE. Psoriasis in monozygotic twins: variations in expression in individuals with identical genetic constitution. Acta dermato-venereologica 1982;62(3):229-36.
15. Duffy DL, Spelman LS, Martin NG. Psoriasis in Australian twins. Journal of the American Academy of Dermatology 1993;29(3):428-34.
16. Trembath RC, Clough RL, Rosbotham JL, et al. Identification of a major susceptibility locus on chromosome 6p and evidence for further disease loci revealed by a two stage genome-wide search in psoriasis. Human molecular genetics 1997;6(5):813-20.
17. Helms C, Saccone NL, Cao L, et al. Localization of PSORS1 to a haplotype block harboring HLA-C and distinct from corneodesmosin and HCR. Human genetics 2005;118(3-4):466-76.
18. Gudjonsson JE, Karason A, Runarsdottir EH, et al. Distinct clinical differences between HLA-Cw*0602 positive and negative psoriasis patients--an analysis of 1019 HLA-C- and HLA-B-typed patients. The Journal of investigative dermatology 2006;126(4):740-5.
19. Prens EP, Benne K, van Damme J, et al. Interleukin-1 and interleukin-6 in psoriasis. The Journal of investigative dermatology 1990;95(6 Suppl):121S-4S.
20. Schottelius AJ, Moldawer LL, Dinarello CA, Asadullah K, Sterry W, Edwards CK, 3rd. Biology of tumor necrosis factor-alpha- implications for psoriasis. Experimental dermatology 2004;13(4):193-222.

21. Torre-Amione G, Kapadia S, Lee J, et al. Tumor necrosis factor-alpha and tumor necrosis factor receptors in the failing human heart. Circulation 1996;93(4):704-11.
22. Kubota T, McTiernan CF, Frye CS, et al. Dilated cardiomyopathy in transgenic mice with cardiac-specific overexpression of tumor necrosis factor-alpha. Circulation research 1997;81(4):627-35.
23. Campalani E, Allen MH, Fairhurst D, et al. Apolipoprotein E gene polymorphisms are associated with psoriasis but do not determine disease response to acitretin. The British journal of dermatology 2006;154(2):345-52.
24. Eichner JE, Dunn ST, Perveen G, Thompson DM, Stewart KE, Stroehla BC. Apolipoprotein E polymorphism and cardiovascular disease: a HuGE review. American journal of epidemiology 2002;155(6):487-95.
25. Yamauchi PS, Rizk D, Kormeili T, Patnaik R, Lowe NJ. Current systemic therapies for psoriasis: where are we now? Journal of the American Academy of Dermatology 2003;49(2 Suppl):S66-77.
26. Dierkes J, Westphal S. Effect of drugs on homocysteine concentrations. Seminars in vascular medicine 2005;5(2):124-39.
27. van Ede AE, Laan RF, Rood MJ, et al. Effect of folic or folinic acid supplementation on the toxicity and efficacy of methotrexate in rheumatoid arthritis: a forty-eight week, multicenter, randomized, double-blind, placebo-controlled study. Arthritis and rheumatism 2001;44(7):1515-24.
28. Lebwohl M. A clinician's paradigm in the treatment of psoriasis. Journal of the American Academy of Dermatology 2005;53(1 Suppl 1):S59-69.
29. Griffiths CE, Dubertret L, Ellis CN, et al. Ciclosporin in psoriasis clinical practice: an international consensus statement. The British journal of dermatology 2004;150 Suppl 67:11-23.
30. Katz HI, Waalen J, Leach EE. Acitretin in psoriasis: an overview of adverse effects. Journal of the American Academy of Dermatology 1999;41(3 Pt 2):S7-S12.
31. de Jong R, Bezemer AC, Zomerdijk TP, van de Pouw-Kraan T, Ottenhoff TH, Nibbering PH. Selective stimulation of T helper 2 cytokine responses by the anti-psoriasis agent monomethylfumarate. European journal of immunology 1996;26(9):2067-74.
32. Hoefnagel JJ, Thio HB, Willemze R, Bouwes Bavinck JN. Long-term safety aspects of systemic therapy with fumaric acid esters in severe psoriasis. The British journal of dermatology 2003;149(2):363-9.
33. Mrowietz U, Christophers E, Altmeyer P. Treatment of psoriasis with fumaric acid esters: results of a prospective multicentre study. German Multicentre Study. The British journal of dermatology 1998;138(3):456-60.
34. Vis M, Nurmohamed MT, Wolbink G, et al. Short term effects of infliximab on the lipid profile in patients with rheumatoid arthritis. The Journal of rheumatology 2005;32(2):252-5.
35. Irace C, Mancuso G, Fiaschi E, Madia A, Sesti G, Gnasso A. Effect of anti TNFalpha therapy on arterial diameter and wall shear stress and HDL cholesterol. Atherosclerosis 2004;177(1):113-8.
36. Rocha-Pereira P, Santos-Silva A, Rebelo I, Figueiredo A, Quintanilha A, Teixeira F. Dislipidemia and oxidative stress in mild and in severe psoriasis as a risk for cardiovascular disease. Clinica chimica acta; international journal of clinical chemistry 2001;303(1-2):33-9.
37. Reynoso-von Drateln C, Martinez-Abundis E, Balcazar-Munoz BR, Bustos-Saldana R, Gonzalez-Ortiz M. Lipid profile, insulin secretion, and insulin sensitivity in psoriasis. Journal of the American Academy of Dermatology 2003;48(6):882-5.
38. Lindegard B. Diseases associated with psoriasis in a general population of 159,200 middle-aged, urban, native Swedes. Dermatologica 1986;172(6):298-304.
39. Inerot A, Enerback C, Enlund F, et al. Collecting a set of psoriasis family material through a patient organisation; clinical characterisation and presence of additional disorders. BMC dermatology [electronic resource] 2005;5:10.
40. Bonifati C, Mussi A, Carducci M, et al. Endothelin-1 levels are increased in sera and lesional skin extracts of psoriatic patients and correlate with disease severity. Acta dermato-venereologica 1998;78(1):22-6.

41. Sowers JR. Hypertension, angiotensin II, and oxidative stress. The New England journal of medicine 2002;346(25):1999-2001.
42. Ho VC. The use of ciclosporin in psoriasis: a clinical review. The British journal of dermatology 2004;150 Suppl 67:1-10.
43. Naldi L, Chatenoud L, Linder D, et al. Cigarette smoking, body mass index, and stressful life events as risk factors for psoriasis: results from an Italian case-control study. The Journal of investigative dermatology 2005;125(1):61-7.
44. Rucevic I, Perl A, Barisic-Drusko V, Adam-Perl M. The role of the low energy diet in psoriasis vulgaris treatment. Collegium antropologicum 2003;27 Suppl 1:41-8.
45. Wellen KE, Hotamisligil GS. Obesity-induced inflammatory changes in adipose tissue. The Journal of clinical investigation 2003;112(12):1785-8.
46. Panagiotakos DB, Pitsavos C, Yannakoulia M, Chrysohoou C, Stefanadis C. The implication of obesity and central fat on markers of chronic inflammation: The ATTICA study. Atherosclerosis 2005;183(2):308-15.
47. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW, Jr. Obesity is associated with macrophage accumulation in adipose tissue. The Journal of clinical investigation 2003;112(12):1796-808.
48. James WPT, Jackson-Leach R, Ni Mhurchu C, et al. Overweight and obesity (high body mass index). In: Ezzati M,Lopez AD, Rodgers A, Murray CJL, eds. Comparative quantification of health risks: global and regional burden of disease attributable to selected major risk factors, vol 1. Geneva: WHO 2004:497-596.
49. Kannel WB, McGee D, Gordon T. A general cardiovascular risk profile: the Framingham Study. The American journal of cardiology 1976;38(1):46-51.
50. Hotamisligil GS, Peraldi P, Budavari A, Ellis R, White MF, Spiegelman BM. IRS-1-mediated inhibition of insulin receptor tyrosine kinase activity in TNF-alpha- and obesity-induced insulin resistance. Science 1996;271(5249):665-8.
51. Paolisso G, Valentini G, Giugliano D, et al. Evidence for peripheral impaired glucose handling in patients with connective tissue diseases. Metabolism: clinical and experimental 1991;40(9):902-7.
52. Binazzi M, Calandra P, Lisi P. Statistical association between psoriasis and diabetes: further results. Archives for dermatological research 1975;254(1):43-8.
53. Herron MD, Hinckley M, Hoffman MS, et al. Impact of obesity and smoking on psoriasis presentation and management. Archives of dermatology 2005;141(12):1527-34.
54. Fortes C, Mastroeni S, Leffondre K, et al. Relationship between smoking and the clinical severity of psoriasis. Archives of dermatology 2005;141(12):1580-4.
55. Ryder MI, Saghizadeh M, Ding Y, Nguyen N, Soskolne A. Effects of tobacco smoke on the secretion of interleukin-1beta, tumor necrosis factor-alpha, and transforming growth factor-beta from peripheral blood mononuclear cells. Oral microbiology and immunology 2002;17(6):331-6.
56. Okubo Y, Koga M. Peripheral blood monocytes in psoriatic patients overproduce cytokines. Journal of dermatological science 1998;17(3):223-32.
57. Flisiak I, Chodynicka B, Porebski P, Flisiak R. Association between psoriasis severity and transforming growth factor beta(1) and beta (2) in plasma and scales from psoriatic lesions. Cytokine 2002;19(3):121-5.
58. Aicher A, Heeschen C, Mohaupt M, Cooke JP, Zeiher AM, Dimmeler S. Nicotine strongly activates dendritic cell-mediated adaptive immunity: potential role for progression of atherosclerotic lesions. Circulation 2003;107(4):604-11.
59. Briganti S, Picardo M. Antioxidant activity, lipid peroxidation and skin diseases. What's new. J Eur Acad Dermatol Venereol 2003;17(6):663-9.
60. Madamanchi NR, Hakim ZS, Runge MS. Oxidative stress in atherogenesis and arterial thrombosis: the disconnect between cellular studies and clinical outcomes. J Thromb Haemost 2005;3(2):254-67.

61. Rocha-Pereira P, Santos-Silva A, Rebelo I, Figueiredo A, Quintanilha A, Teixeira F. The inflammatory response in mild and in severe psoriasis. The British journal of dermatology 2004;150(5):917-28.
62. Clarke R, Lewington S. Homocysteine and coronary heart disease. Seminars in vascular medicine 2002;2(4):391-9.
63. Vanizor Kural B, Orem A, Cimsit G, Uydu HA, Yandi YE, Alver A. Plasma homocysteine and its relationships with atherothrombotic markers in psoriatic patients. Clinica chimica acta; international journal of clinical chemistry 2003;332(1-2):23-30.
64. Blann AD. Endothelial cell activation, injury, damage and dysfunction: separate entities or mutual terms? Blood Coagul Fibrinolysis 2000;11(7):623-30.
65. Vita JA, Keaney JF, Jr. Endothelial function: a barometer for cardiovascular risk? Circulation 2002;106(6):640-2.
66. Blann AD, Lip GY. The endothelium in atherothrombotic disease: assessment of function, mechanisms and clinical implications. Blood Coagul Fibrinolysis 1998;9(4):297-306.
67. Boneu B, Abbal M, Plante J, Bierme R. Letter: Factor-VIII complex and endothelial damage. Lancet 1975;1(7922):1430.
68. Corretti MC, Anderson TJ, Benjamin EJ, et al. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force. Journal of the American College of Cardiology 2002;39(2):257-65.
69. Berrettini M, Parise P, Constantini V, Grasselli S, Nenci GG. Platelet activation in psoriasis. Thrombosis and haemostasis 1985;53(2):195-7.
70. Vila L, Cullare C, Sola J, Puig L, de Castellarnau C, de Moragas JM. Cyclooxygenase activity is increased in platelets from psoriatic patients. The Journal of investigative dermatology 1991;97(5):922-6.
71. Gawaz M, Langer H, May AE. Platelets in inflammation and atherogenesis. The Journal of clinical investigation 2005;115(12):3378-84.
72. Laufs U, La Fata V, Plutzky J, Liao JK. Upregulation of endothelial nitric oxide synthase by HMG CoA reductase inhibitors. Circulation 1998;97(12):1129-35.
73. Kwak B, Mulhaupt F, Myit S, Mach F. Statins as a newly recognized type of immunomodulator. Nature medicine 2000;6(12):1399-402.
74. Neuhaus O, Stuve O, Zamvil SS, Hartung HP. Are statins a treatment option for multiple sclerosis? Lancet neurology 2004;3(6):369-71.
75. Youssef S, Stuve O, Patarroyo JC, et al. The HMG-CoA reductase inhibitor, atorvastatin, promotes a Th2 bias and reverses paralysis in central nervous system autoimmune disease. Nature 2002;420(6911):78-84.
76. Hakamada-Taguchi R, Uehara Y, Kuribayashi K, et al. Inhibition of hydroxymethylglutaryl-coenzyme a reductase reduces Th1 development and promotes Th2 development. Circulation research 2003;93(10):948-56.
77. Choi HK, Hernan MA, Seeger JD, Robins JM, Wolfe F. Methotrexate and mortality in patients with rheumatoid arthritis: a prospective study. Lancet 2002;359(9313):1173-7.
78. Pearson TA, Blair SN, Daniels SR, et al. AHA Guidelines for Primary Prevention of Cardiovascular Disease and Stroke: 2002 Update: Consensus Panel Guide to Comprehensive Risk Reduction for Adult Patients Without Coronary or Other Atherosclerotic Vascular Diseases. American Heart Association Science Advisory and Coordinating Committee. Circulation 2002;106(3):388-91.

Chapter 4

Psoriasis may not be an independent predictor for the use of cardiovascular and antidiabetic drugs: results from a 5-year prevalence study

Marlies Wakkee
Willemijn Meijer
H.A. Martino Neumann
Ron M.C. Herings
Tamar Nijsten

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Abstract

Most studies investigating the association between psoriasis and cardiovascular disease showed a significant relationship. This comparison study investigated the association between psoriasis and prevalent use of cardiovascular drugs. Drug exposure data were extracted between 1998 and 2006 from the PHARMO-Record Linkage System database. Psoriasis patients were selected using an algorithm of hospitalization and drug dispensing records specific for psoriasis and matched to controls for gender, age and time-period. Of the records of 2.5 million Dutch residents, 9,804 (0.4%) psoriasis patients and 15,288(0.6%) controls were selected. Psoriasis patients used significantly more antihypertensives, anticoagulant and antiplatelet agents, digoxin, nitrates, lipid lowering and antidiabetic drugs than the reference population during a 5-year period observation. In a multiple linear regression model adjusting for the number of unique drugs used, psoriasis was no longer significantly associated with any of these drug classes. Psoriasis patients used more cardiovascular related drugs, but surveillance bias appears to affect this association considerably.

Introduction

Psoriasis is becoming associated more and more with increased cardiovascular morbidity and mortality, and consequently there is a trend to "upgrade" psoriasis from a cutaneous to a systemic disease. Although the first studies suggesting an association between psoriasis and cardiovascular disease (CVD) date from 1973, recently multiple observational studies have tested the hypothesis that psoriasis is a systemic disease that is not restricted to the skin.[1-5] The findings of most, but not all, studies demonstrate an increased risk of CVD, especially in patients with severe psoriasis. A Finnish and US cohort study suggested that the increased mortality rate in psoriasis patients was not due to excess CVD mortality but to liver disease and/or alcohol psychosis.[6, 7] A Swedish population-based cohort study demonstrated an increased risk of CVD mortality only among patients who had been hospitalized for psoriasis, but not among outpatients.[8] Studies that analysed the UK General Practitioner Research Database (GPRD) observed an increased risk of myocardial infarction, especially in younger psoriasis patients, and an almost two-fold higher mortality rate in patients who used systemic psoriasis therapies, but not in milder cases compared with controls.[9, 10] Interestingly, a recent study using the same database showed no difference in the likelihood of having used anti-hypertensive, lipid-lowering and anti-diabetic drugs between psoriasis patients and their matched controls.[11] The observed differences between the observational studies may be related to different study designs, selection procedures, outcomes, follow-up times and available information on confounders.[12]

It has been argued that low-grade chronic inflammation with elevated levels of tumour necrosis factor (TNF)-alpha is the common pathway of psoriasis, CVD and metabolic syndrome.[9] However, the explanation of the association between psoriasis, metabolic syndrome and CVD is likely to be more complex and multifactorial (Fig. 1).[13, 14] Most studies show that more severely affected psoriasis patients, often defined as those who have been hospitalized or have used systemic therapies, are at an increased risk of CVD (mortality). This may be due to a higher inflammatory status, but equally may be due to more impaired healthrelated quality of life (HRQoL) and depression, therapyinduced toxicity, and/or increased likelihood of being diagnosed with CVD (i.e. detection bias). This might be important because more than one-third of individuals with hypertension are undiagnosed.[15-17]

The objective of this study is to investigate the association between psoriasis and prevalent use of drugs for CVD and diabetes in a large sample of the general population.

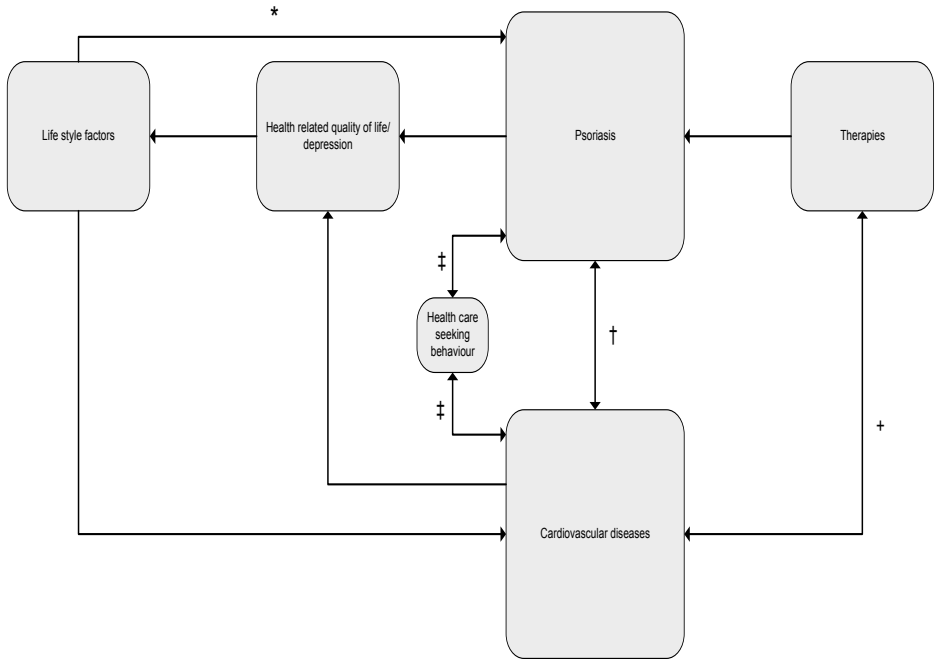

Figure 1. Schematic example of the complex relationship between psoriasis and cardiovascular diseases.

* A few observational studies suggested that several life style factors contribute to the development of psoriasis.[18, 19]

+ Several systemic psoriasis therapies may have cardiovascular side effects (e.g., ciclosporin and hypertension), but these therapies may also alter the inflammatory status of a patient and thus affect CVD.[4] Also, a history of CVD affects treatment options and may therefore indirectly have an effect on the psoriasis severity.

‡ Once a patients seeks care for a medical problem (e.g. psoriasis) they are likely to be diagnosed with other diseases (e.g. hypertension) as well and to seek care for other complaints more easily than patients who have not visited a physician.

† Another hypothesis is that psoriasis may result in a innate increased risk of CVD by the inflammatory process and there may even be a comparable genetic pathogenesis.[4]

Materials and methods

Data source

This study was conducted with data from the PHARMO Record Linkage System (PHARMO RLS), which consists of several linked databases, including drug dispensing, hospital and clinical laboratory records from more than 2.5 million individuals who were ever living in defined areas in the Netherlands.[20-22] The drug dispensing histories contain data on the dispensed drug, type of prescriber, dispensing date, amount dispensed, prescribed dose regimens, and the legend duration of use (prescription length). All drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification.[23] The hospital records include detailed information

concerning primary and secondary diagnoses, procedures, and dates of hospital admission and discharge. All diagnoses are coded according to the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM).[24] In a subset of the PHARMO RLS, medical records from the general practitioner (GP) were available, including among others diagnoses coded according to the International Classification for Primary Care (ICPC).[25]

Study design

This was a comparative prevalence study in which prevalent psoriasis patients were compared with a reference population with regard to outcomes in terms of specific drug prescriptions during a period of 5 years.

Study population

Patients with psoriasis were identified from the PHARMO database using an algorithm based on recorded hospitalizations and drug dispensing records. This algorithm comprised five steps (hospitalizations for psoriasis, psoralen-ultraviolet A (PUVA) treatment, topical treatments, systemic treatments, and exclusions). For each patient, the likelihood of psoriasis was classified as possible, probable or definite at the first four algorithm steps, based on the specificity for the diagnosis psoriasis. Only those classified as definite psoriasis during at least one of these four steps were eligible for inclusion. Details of the algorithm: patients with a hospital discharge diagnosis of psoriasis and/or psoriatic arthritis (ICD 696.1 and 696.0, respectively) were classified as definite psoriasis (step 1), patients who received psoralen prescriptions (for PUVA therapy) were classified as definite psoriasis (step 2), patients who received calcipotriol, calcitriol or ditranol, fumaric acid or efalizumab were classified as definite psoriasis (step 3 and 4); and patients who did not fill any of the above-mentioned prescriptions but who received prescriptions for topical corticosteroids or coal tar (step 3), systemic glucocorticosteroids (although not considered standard therapy according the Dutch psoriasis guidelines), retinoids, immunosuppressants (methotrexate or cyclosporine), adalimumab, etanercept and/or infliximab (step 4) were classified as possible or probable psoriasis.[26] UVB therapy was not assessed in this study because it does not require a pharmacy prescription nor hospitalizations. In the fifth step of the algorithm, all psoriasis patients classified as definite psoriasis based on steps 1–4, who were also hospitalized in the period 1998 to 2006 for skin conditions other than psoriasis were excluded. Other criteria were: presence in the database during 1998 to 2006 for at least 6 months before first mention in the algorithm, age at start of follow-up (i.e. index date) ≥ 18 years and an available follow-up duration of at least 5 years. Diseases that could affect the development of psoriasis, the psoriasis severity, and/or the use of the studied drugs were excluded based on the corresponding ICD-codes (i.e. human immunodeficiency virus, immune disorders, inflammatory bowel diseases, hepatitis B and C, multiple sclerosis, rheumatoid arthritis and status after organ

transplant). Reference subjects were eligible for inclusion if they were not classified as either definite, probable or possible psoriasis using the same algorithm applied to all individuals in the database (to avoid false-negative cases), if they could be matched for age and gender to a patient classified as definite psoriasis, and if they were present in the database during 1998 to 2006 for at least 6 months before the index date of the patient they were eligible to be matched to, and had at least 5 years of follow-up. Furthermore, subjects from the reference population were excluded if they were hospitalized for other dermatological diseases as defined in step 5 of the algorithm, or if they had one of the diseases or conditions listed above.

Matching

Psoriasis patients were matched in a 1:2 ratio for gender, age (in years) and similar time and duration of eligibility in PHARMO RLS to controls from the reference population. No psoriasis patient was sampled as a reference subject; however, subjects from the reference population could be matched to more than one psoriasis patient.

Classification of severity of psoriasis

Each included patient with psoriasis was classified into either mild or moderate/severe disease. Mild psoriasis was defined as prior use of topical therapies only and patients with moderate to severe psoriasis had at least a prior dispensing of psoralen, a systemic anti-psoriatic drug and/or a recorded hospitalization for psoriasis (including psoriatic arthritis).

Validation of the algorithm to identify patients with psoriasis

For a subset of 1,211 patients with definite psoriasis and 2,227 matched controls, electronic medical records were available from their GP. Among the definite psoriasis patients, 1,174 (94%) were classified as such based on prescriptions of topical treatments (algorithm step 3). The GPs' records were searched for the ICPC code S91 ("psoriasis") in the medical Journal field, Diagnosis list, Problem list, and Referral field. Among the 1,211 patients classified as definite psoriasis, 664 (54.8%) had a recorded ICPC code S91 ("psoriasis"), whereas among the 2,227 matched controls, 12 subjects (0.5%) had a recorded ICPC code S91 ("psoriasis") in these fields. This yields a total of 676 (19.7%) diagnostic codes S91 ("psoriasis") recorded by the GPs out of 3,438 subjects in the sample (patients and controls). Considering the GPs' record of the coded diagnosis S91 ("psoriasis") as a surrogate gold standard, the sensitivity of the algorithm was calculated as 98.2% (664/676), specificity 80.2% (2,215/2,762), positive predictive value as 54.8% (664/1,211) and negative predictive value as 99.5% (2,215/2,227). However, the data of the GPs remain a surrogate gold standard, since some psoriasis patients regularly visit their medical specialist, but are rarely seen by their GP.

Follow-up period

All subjects were in the database for at least 6 months before the index date and were subsequently followed up for 5 years. A schematic example of a case with 6 months of history and a 5-year follow-up period is shown in Fig. 2. The index date, which reflects the first available date of a prescription or hospitalization associated with psoriasis, was included to ensure that there was at least one period of disease activity. A 5-year period was chosen to ensure sufficient follow-up to develop the co-morbidities of interest.

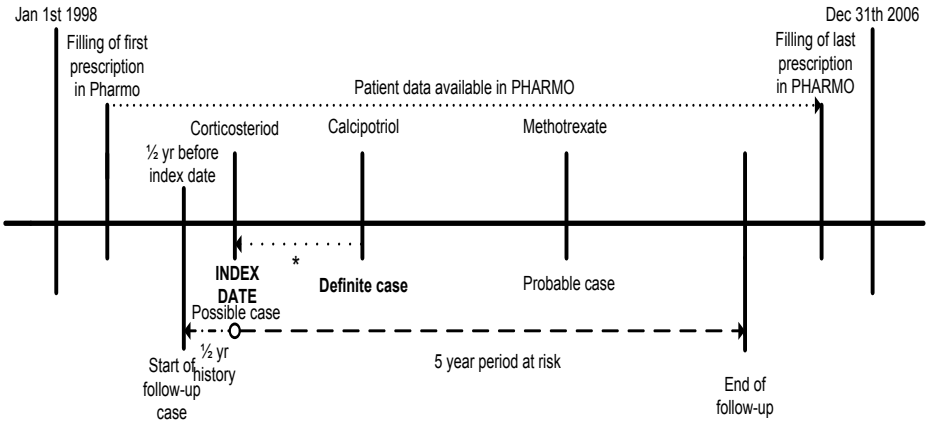

Figure 2. Schematic example of a psoriasis patient with 6 months of history and a 5-year follow-up period As registered in PHARMO Record Linkage System.

Study outcome: cardiovascular or anti-diabetic drug prescriptions

The presence of CVD or diabetes mellitus was determined by examining the prescriptions for the associated drugs in all subjects during the 5 years after the index date. The studied drugs were anti-hypertensive medication, including beta-blockers, calcium channel blockers, ACE-inhibitors, angiotensin-II receptor antagonists, diuretics (ATC codes: C07, C08, C09 and C03), vitamin K antagonists/oral anti-coagulants and platelet aggregation inhibitors excluding heparin (ATC codes: B01AA and B01AC), digoxin (C01AA05), nitrates (C01DA), lipidlowering drugs including statins and fibrates (C10AA and C10AB) and anti-diabetic drugs including oral anti-diabetics and insulin (A10B and A10A).

Potential confounders

The association between psoriasis, CVD and metabolic syndrome is affected by multiple confounders, such as HRQoL, lifestyle factors, prior psoriasis therapies used and degree of healthcare utilization (Fig. 1). In an attempt to adjust for healthcare- and pharmacy-seeking

behaviour, the total number of unique prescriptions (i.e. number of different ATC codes on ATC-3 level) recorded in the database during the 6 months prior to the index date was calculated for each eligible individual. This timeframe was chosen to obtain a reliable representation of the different drugs used, since it comprises twice the maximum prescription period of 90 days. Two different multivariate logistic regression models were applied. Topical drugs and pain medication were excluded from the total number of unique ATC codes in both multivariate analyses, because these drugs are likely to be associated with psoriasis, resulting in an unbalanced correction.

The final, a previously selected multivariate model, additionally excluded the specific drug class studied in each analysis (e.g. dependent outcome) from the total unique ATC codes. Lipid-lowering, anti-diabetic drugs and anti-depressants can be considered as proxies for increased abdominal obesity and body mass index (BMI), diabetes and depression, respectively. Therefore, the included ATC codes in this model allowed partial adjustment for BMI, diabetes and depression. However, to investigate whether including all other cardiovascular drugs in this model may have led to over-adjustment, a second analysis was conducted in which all prior CVD and metabolic drug prescriptions were excluded. No information was available on HRQoL or lifestyle factors, such as physical exercise, diet, smoking and alcohol consumption.

Statistical analysis

Continuous variables are presented as mean values with standard deviations or median values and interquartile range and were tested for statistical significant differences using the Student's t-test or the Mann-Whitney U test as appropriate. The proportion of psoriasis patients and controls using cardiovascular and anti-diabetic drugs were compared using a χ^2 test. The χ^2 test for linear trend was used to test for significant differences between controls, and patients with mild, and moderate to severe psoriasis. For each drug class separately, a logistic regression model was used to calculate (un)adjusted odds ratios (OR) and 95% confidence intervals (CI) for the association between psoriasis and the studied drug class (i.e. dependent variable). Because case and controls were matched for gender, age and index date, healthcare consumption (total unique ATC codes) was the only variable adjusted for in the multivariate model. All statistical tests were two-sided with a p-value < 0.05 considered statistically significant. Analyses were performed using SPSS 15.0 (SPSS Inc. Chicago, IL, USA). The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines were used to ensure the reporting of this observational study.[12]

Results

Study population

Our algorithm identified 9,804 eligible people with a definite diagnosis of psoriasis, who were treated with specific anti-psoriatic drugs or were hospitalized for their psoriasis, as well as 15,288 matched subjects for the reference population. The 5-year prevalence of (definite) psoriasis in the study population was estimated to be 0.4%. In both populations, 47% were male and the mean age was 49 years (Table 1). Compared with the reference population, psoriasis patients were significantly more likely to have used a higher number of unique drugs in the 180 days prior to the index date ($p < 0.001$, Table 1). Ninety percent of the 9,804 psoriasis patients were classified as having mild psoriasis (i.e. use of topical therapies only during 5 years of observation) and 10% had used systemic psoriasis therapies and were considered to have moderate

Table I. Baseline characteristics of the study population at index date[a]

Variable	Psoriasis patients	Reference population
Total no. (%)	9804 (39.1)	15 288 (60.9)
Gender, *n* (%)		
Male (%)	4607 (47.0)	7130 (46.6)
Female (%)	5197 (53.0)	8158 (53.4)
Age in years		
Mean (SD)	49.0 (15.1)	48.7 (14.7)
Median (IQR)	49.0 (37.0;60.0)	49.0 (37.0;60.0)
Total person-years of follow-up, *n*	49 020	76 440
Health care consumption, median (IQR)[b]	2 (1;4)	1 (0;3)
Health care consumption corrected, median (IQR)[c]	2 (1;3)[d]	1 (0;2)[d]
Psoriasis severity, *n* (%)[e]		
Mild	8835 (90.1)	0 (0.0)
Moderate to severe	969 (9.9)	0 (0.0)
Therapies ever used in 5 year follow-up, *n* (%)		0 (0.0)
Topical antipsoriatic therapies	9744 (99.4)	
PUVA-therapy	303 (3.1)	
Methotrexate	65 (0.7)	
Ciclosporin	251 (2.6)	
Acitretin	490 (5.0)	
Biologics[f]	14 (0.1)	

[a] The earliest available date an antipsoriatic drug was prescribed or a hospitalization for psoriasis occurred in patients with psoriasis and for controls a prescription or medical diagnose within 30 days of this date.

[b] Unique number of drugs on Anatomical Therapeutic Chemical (ATC)-3 level in 180 days before index date minus all topical therapies.

[c] Unique number of drugs on ATC-3 level in 180 days before index date minus all topical therapies and pain medication.

[d] Mann-Whitney U test, $P < 0.001$ for psoriasis patients versus the reference population.

[e] mild psoriasis was defined as prior use of topical therapies only and moderate to severe psoriasis as ever use of systemic drugs including PUVA and/or hospitalization for psoriasis.

[f] adalimumab (n=1), efalizumab (n= 2), etanercept (n= 11).

SD, standard deviation; IQR, interquartile range (25th and 75th percentile shown); PUVA, psoralen plus ultraviolet-A

to severe psoriasis. During the 5-year period, 5% of the psoriasis patients filled a prescription for acitretin, 3.1% for psoralen, 2.6% for ciclosporin and less than 1% for methotrexate or a biologic (Table 1). Of the patients with mild and moderate to severe psoriasis, 10% and 20%, respectively, had used systemic glucocorticosteroids (e.g. prednisone or dexamethasone) during the follow-up period.

Use of cardiovascular drugs and anti-diabetics

Descriptive and univariate analyses. Table 2 presents the 5-year prevalence of all cardiovascular and anti-diabetic drugs among the psoriasis patients and matched reference population

Table II. Five year prevalence of cardiovascular and antidiabetic drugs in patients with psoriasis and the matched reference population.

	Reference population[a] n=15288, *n* (%)	All psoriasis patients n=9804, *n* (%)	*p*-value All psoriasis patients vs reference population	Patients with mild psoriasis[b] n=8835, *n* (%)	Patients with moderate to severe psoriasis[c] n=969, *n* (%)	*p*-value for trend[d]
Antihypertensive drugs total	4619 (30.2)	3413 (34.8)	<0.001	3079 (34.9)	334 (34.5)	<0.001
Beta-blocker	3031 (19.8)	2094 (21.4)	0.003	1914 (21.7)	180 (18.6)	0.042
ACE-inhibitor or ATII- antagonist	2189 (14.3)	1709 (17.4)	<0.001	1172 (16.1)	537 (21.2)	<0.001
Ca-antagonist	1244 (8.1)	1095 (11.2)	<0.001	968 (11.0)	127 (13.1)	<0.001
Diuretics	1896 (12.4)	1639 (16.7)	<0.001	1461 (16.5)	178 (18.4)	<0.001
Anticoagulants/ Antiplateled agents total	2421 (15.8)	1848 (18.8)	<0.001	1670 (18.9)	178 (18.4)	<0.001
Oral anticoagulants	717 (4.7)	538 (5.5)	0.005	484 (5.5)	54 (5.6)	0.007
Platelet aggregation inhibitors	1960 (12.8)	1534 (15.6)	<0.001	1396 (15.8)	138 (14.2)	<0.001
Digoxin	199 (1.3)	177 (1.8)	0.001	157 (1.8)	20 (2.1)	0.001
Nitrates	1090 (7.1)	933 (9.5)	<0.001	845 (9.6)	88 (9.1)	<0.001
Lipid lowering drugs total	2062 (13.5)	1521 (15.5)	<0.001	1379 (15.6)	142 (14.7)	<0.001
Statins	2002 (13.1)	1481 (15.1)	<0.001	1344 (15.2)	137 (14.1)	<0.001
Fibrates	97 (0.6)	89 (0.9)	0.014	75 (0.8)	14 (1.4)	0.003
Anti-diabetic drugs total	939 (6.1)	706 (7.2)	0.001	620 (7.0)	86 (8.9)	<0.001
Oral antidiabetic drugs	798 (5.2)	601 (6.1)	0.002	527 (6.0)	74 (7.6)	<0.001
Insulin	314 (2.1)	263 (2.7)	0.001	232 (2.6)	31 (3.2)	0.001

[a] Controls matched for age, gender and index date without a possible, probable or definite psoriasis diagnosis.

[b] Mild psoriasis is defined as patients with no more than prescriptions for topical anti-psoriatic therapies.

[c] Moderate to severe psoriasis is defined as patients who used, systemic anti-psoriatic drugs including psoralens and/or were hospitalised for psoriasis.

[d] Chi square trend test for linear trend between controls, and patients with mild and moderate to severe psoriasis.

ATII-antagonist, Angiotensin-II receptor inhibitor; Ca-antagonist, Calcium channel blocker.

provided with a chi-square test and a trend test to determine the presence of a significant linear trend across psoriasis severity (i.e. no, mild, and moderate to severe psoriasis). In addition, all cardiovascular and anti-diabetic drugs were significantly more frequently prescribed among patients with psoriasis than among the age and sex-matched reference population, a significant linear trend was observed for psoriasis severity. For all study drugs, the absolute difference in prevalent use observed between psoriasis patients and controls and between psoriasis severity categories was less than 5%. The largest difference in proportion of users between controls and psoriasis patients was noted for the anti-hypertensive drugs (30.2% vs. 34.8%, $p < 0.001$), especially for diuretics and calcium channel blockers. Except for beta-blockers, nitrates, platelet aggregation inhibitors and statins, the proportion of patients increased significantly with disease severity (e.g. 21.7% of patients with mild vs. 18.6% of those with moderate to severe psoriasis used beta-blockers, $p = 0.026$). Compared with controls, a significantly larger proportion of psoriasis patients used anti-coagulants or platelet aggregation inhibitors (15.8% vs. 18.8%, $p < 0.001$), lipid-lowering drugs (13.5% vs. 15.5%, $p < 0.001$) and anti-diabetic drugs (6.1% vs. 7.2%, $p = 0.001$). The prevalence of using these drug classes increased significantly with psoriasis severity. Univariate logistic regression analyses showed that psoriasis patients had approximately 20% higher odds of using drugs for hypertension, hyperlipidaemia and diabetes compared with people without psoriasis (Table 3). Compared with the matched references, psoriasis patients had almost 40% higher odds of having used calcium channel blockers (adjusted OR = 1.42; 95% CI 1.30–1.55).

Multivariate analyses

After adjusting for the variable that comprised both a proxy for healthcare consumption (i.e. unique number of ATC codes in 6 months prior to index date) and also partially adjusted for BMI, diabetes and depression, none of the associations between psoriasis and the studied drugs remained significant (Table 3), except for calcium channel blockers and diuretics (adjusted OR = 1.10; 95% CI 1.01–1.21 and adjusted OR = 1.13; 95% CI 1.04–1.21, respectively). Stratifying for psoriasis severity showed that the observed difference for diuretics remained significant for mild psoriasis, but was non-significant for the calcium channel blockers in both categories of psoriasis severity. The likelihood of receiving beta-blockers was significantly lower in patients with moderate to severe psoriasis compared with controls (adjusted OR = 0.76, 95% CI 0.61–0.95). The additional multivariate analysis, which excluded all CVD and metabolic drugs from the unique number of prior prescriptions lowered the ORs less strongly. According to these adjustments, patients with psoriasis had a 1.1–1.2 greater odds of using anti-hypertensives, anti-coagulants and anti-platelet agents, nitrates and lipid-lowering drugs.

Table III. Prevalence odds ratios of dispensings of cardiovascular drugs and antidiabetics in patients with psoriasis versus controls and in patients with mild as well as moderate to severe psoriasis patients versus controls.

Study outcome: drug dispensing	All psoriasis patients (n= 9804) vs controls			Mild psoriasis (n= 969) vs controls[d]	Moderate to severe psoriasis (n= 8835) vs controls[e]
	Unadjusted OR[a] (95% CI)	Adjusted OR[b] (95% CI)	Adjusted OR excluding all prior CVD drugs[c] (95% CI)	Adjusted OR[b] (95% CI)	Adjusted OR[b] (95% CI)
Antihypertensive drugs	**1.23 (1.17-1.30)**	1.02 (0.96-1.07)	**1.09 (1.03-1.16)**	1.03 (0.97-1.09)	0.92 (0.76-1.10)
Beta-blocker	**1.10 (1.03-1.17)**	0.95 (0.89-1.01)	1.02 (0.96-1.09)	0.97 (0.91-1.04)	**0.76 (0.61-0.95)**
ACE-inhibitor or ATII- antagonist	**1.26 (1.18-1.35)**	1.05 (0.98-1.13)	**1.14 (1.06-1.22)**	1.07 (0.99-1.15)	0.87 (0.69-1.11)
Ca-antagonist	**1.42 (1.30-1.55)**	**1.10 (1.01-1.21)**	**1.21 (1.11-1.32)**	1.08 (0.99-1.19)	1.30 (0.97-1.74)
Diuretics	**1.13 (1.04-1.21)**	**1.13 (1.04-1.21)**	**1.18 (1.09-1.27)**	**1.12 (1.04-1.21)**	1.16 (0.91-1.48)
Anticoagulants/ Antiplateled agents	**1.23 (1.16-1.32)**	0.96 (0.90-1.03)	**1.10 (1.03-1.18)**	0.97 (0.90-1.04)	0.92 (0.73-1.17)
Digoxin	**1.39 (1.14-1.71)**	0.99 (0.80-1.23)	1.09 (0.88-1.35)	0.95 (0.76-1.19)	1.67 (0.78-3.57)
Nitrates	**1.37 (1.25-1.50)**	0.99 (0.90-1.10)	**1.20 (1.09-1.32)**	1.02 (0.92-1.13)	0.79 (0.57-1.09)
Lipid lowering drugs	**1.18 (1.10-1.27)**	0.96 (0.89-1.03)	**1.11 (1.03-1.19)**	0.97 (0.89-1.04)	0.88 (0.69-1.13)
Anti-diabetic drugs	**1.19 (1.07-1.31)**	0.98 (0.88-1.08)	1.07 (0.96-1.19)	0.97 (0.87-1.08)	1.02 (0.74-1.42)

Statistically significant odds ratios with a P-value < 0.05 are in bold.

a Controls were matched for gender, age, and index date.

b Adjusted for health consumption by using the total number of unique drug prescriptions in 180 days before the index date minus all topical drugs, pain medication and the drug that is being examined.

c Adjusted for health consumption by using the total number of unique drug prescriptions in 180 days before the index date minus all topical drugs, pain medication and all CVD and metabolic syndrome associated drugs.

d Mild psoriasis is defined as patients with no more than prescriptions for topical anti-psoriatic therapies.

e Moderate to severe psoriasis is defined as patients who used, systemic anti-psoriatic drugs including psoralens and/or were hospitalised for psoriasis.

ATII-antagonist, Angiotensin-II receptor inhibitor; Ca-antagonist, Calcium channel blocker; CI, confidence interval; OR, odds ratio.

Discussion

In this large Dutch population-based study, patients with psoriasis had higher prescription rates for all drugs associated with the metabolic syndrome (with an absolute maximum difference of 5%) compared with the reference population, but they were also more likely to have used other prescription drugs. After entering a variable that assessed the number of unique drugs used in the multivariate models, in order to reduce the effect of other co-morbidities and detection bias, none of the associations between psoriasis and drug use remained significant,

except that more severely affected psoriasis patients used less beta- blockers. This is probably because patients with moderate to severe psoriasis are more likely to have received specialized care from dermatologists who are attentive of the possible negative effect of beta-blockers on psoriasis, especially in patients with extensive and/or therapy resistant psoriasis.[27] Nevertheless, one-fifth of the psoriasis patients received a beta-blocker as an antihypertensive therapy.

The study's findings may suggest that not the inflammatory process, but increased healthcare utilization (i.e. surveillance bias) may be an important factor for the higher use of cardiovascular and anti-diabetic drugs in psoriasis patients. Many diseases remain subclinical and unrecognized until a patient for some other reason (e.g. the treatment of psoriasis) seeks medical attention. For example, 30–60% of the people with hypertension and 45% of those with dyslipidaemia are undiagnosed and myocardial infarctions remain clinically unrecognized in a large proportion (21–68%) of elderly patients.[15-17] The consistent finding that psoriasis patients who have been hospitalized and not those who are only treated in outpatient settings are at significantly higher risk of several co-morbidities may confirm the importance of surveillance bias. Altogether, additional healthcare consumption may have a substantial effect on the detection of co-morbidities (including CVD and metabolic syndrome) and the frequency of drug utilization in psoriasis patients.

It can be argued that by adding the number of unique drugs taken (including lipid-lowering, anti-diabetic and anti-depressant drugs) to the multivariate analysis, the results suffered from over-adjustment. Patients were followed from their index date, which is the first available prescription or hospitalization for psoriasis and may therefore have already had psoriasis in the 6 months prior to inclusion, which could also have affected their use of CVD and metabolic drugs. Although prescriptions of the studied drug class (as well as painkillers and topical drugs) were excluded from this variable to minimize possible over-adjustment, there may have been associations between the other prior cardiovascular drugs and the outcome variable. Excluding all cardiovascular drugs from this variable resulted in less comprehensive reductions in the crude ORs than in the initial multivariate analyses (Table 3), suggesting that over-adjustment may have occurred in the initial analyses. However, only the initial analyses allowed for partial adjustment for important cardiovascular risk factors, such as diabetes and obesity. The Pearson's correlations coefficients were comparable for the different CVD and metabolic drugs in the psoriasis population and reference population, separately (range 0.09–0.54 and 0.08–0.52, respectively). This assured equal effects of adjustments in both populations. Adding the initial proxy for healthcare consumption improved the fit of the model (Nagelkerke R-squared statistics increased considerably) and the likelihood ratio tests were significant for all analysis to which this variable was added. In a sensitivity multivariate analysis, the number of hospitalizations in the 5 years of follow-up after the index date were used as an alternative proxy for healthcare consumption. This analysis showed comparable effects as were seen after adjusting

for the unique number of ATC codes. After adjustment only antihypertensives (adjusted OR = 1.13; 95% CI 1.07–1.20) and nitrates (adjusted OR = 1.17; 95% CI 1.07–1.29) were significantly associated with psoriasis. Because the distribution of unique number of ATC codes was less skewed than the number of hospitalizations (64% of the psoriasis population and 56% of the reference population were not hospitalized during these 5 years), the results of the analyses that included number of ATC codes were presented.

One of the strengths of this study is that the study outcome (i.e. drug use) is well documented because a pharmacy database that records filling of prescriptions has been used. However, prescription rates are likely to underestimate the true prevalence of CVDs because of undiagnosed cases, under-treatment and/or poor compliance.[22, 28, 29] The applied algorithm to select psoriasis patients from this population-based database only included definite psoriasis patients in order to reduce the number of false-positive cases. The 5-year psoriasis prevalence was 0.4%, which is lower than the lifetime prevalence in other Western populations, of approximately 2–3%.[30] This discrepancy may be due to the period prevalence, the strict selection criteria of the algorithm, the high percentages of patients not seeking healthcare and/or patients not having received vitamin D derivatives (in a US general population sample of psoriasis patients almost 80% never used calcipotriol).[31] To avoid that false-negative cases (e.g. patients who had received topical corticosteroids, cyclosporine and methotrexate, but without vitamin D derivatives, PUVA, efalizumab or inpatient treatments) would pollute the reference group, all possible and probable psoriasis patients were excluded from the analyses. The 5-year follow-up of all eligible subjects was chosen to select the most optimal time-frame to prevent the exclusion of a substantial proportion of subjects with insufficient follow-up. This time-span increases the likelihood that our study results are reliable representation of the actual prevalence of CVD drug use in the psoriasis patients from the general population. Although the use of CVD drugs is probably one of the first available parameters of a different cardiovascular profile of psoriasis patients, it cannot be excluded that for a significant effect of systemic inflammation on the occurrence of cardiovascular events perhaps even longer follow-up time may had been required. Unfortunately, this algorithm could not include UVB (ultraviolet B), which is among the most commonly used therapies for moderate to severe psoriasis in the Netherlands, since its use does not require a pharmacy visit and was not recorded in one of the other available databases.[26] The lack of UVB information may not have reduced the number of psoriasis patients because most patients who have been exposed to UVB are likely to have used vitamin D derivatives, but may have led to a misclassification bias in psoriasis severity (i.e. patients who have used topical drugs and UVB were categorized as mild and not moderate to severe disease). To minimize the selection of false-positive cases, the study was restricted to definite psoriasis cases. Validating a subsample of the eligible cases showed that 98.2% of the patients who had psoriasis according to the general physician files were also recognized as definite psoriasis patients. This remarkably high sensitivity was accompanied by a reasonable specificity of 80.2%. However, 547 patients

(20%) who were classified as definite psoriasis by our algorithm were also not identified as such by their GP, implicating either that our algorithm was not sufficiently specific or that not every psoriasis patient is registered as such in the GPs' files. Since the patient records were anonomized, we were not able to contact the patients or had any other options for testing the positive predictive value to validate our algorithm. A limitation of using a pharmacy database is that several patients and disease characteristics, such as type and extent of psoriasis, BMI, HRQoL impairment, depression and lifestyle factors, were not available. Because the variable unique number of ATC codes included lipid-lowering, anti-diabetic and anti-depressive drugs, diabetes, depression and, in part, obesity were corrected for in the multivariate model. Adjustment for important confounders remains challenging for each of the epidemiological studies that assessed the association between psoriasis and CVD.[1, 8, 9, 32, 33]

Although the proportion of psoriasis patients using cardiovascular drugs is higher than that of controls, the findings of this large population-based study may indicate that there is no direct relationship between psoriasis and CVD or metabolic syndrome. The discrepancy between the univariate and multivariate analyses illustrates the complexity of studies assessing co-morbidities in psoriasis and suggests that medical surveillance bias, in addition to HRQoL impairment and depression, therapies and lifestyle factors, is an important confounder. Unfortunately, none of the other observational studies that demonstrated psoriasis as an independent risk factor for CVD adjusted for healthcareseeking behaviour or exposure.[8, 9] The ideal study design to further examine the relationship between psoriasis and co-morbidities is to conduct a large prospective cohort study with long follow-up specifically designed to investigate this relationship in patients first diagnosed with psoriasis.

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References

1. McDonald CJ, Calabresi P. Occlusive vascular disease in psoriatic patients. N Engl J Med 1973;288(17):912.
2. Warrington KJ, Kent PD, Frye RL, et al. Rheumatoid arthritis is an independent risk factor for multivessel coronary artery disease: a case control study. Arthritis Res Ther 2005;7(5):R984-91.
3. Maradit-Kremers H, Nicola PJ, Crowson CS, Ballman KV, Gabriel SE. Cardiovascular death in rheumatoid arthritis: a population-based study. Arthritis Rheum 2005;52(3):722-32.
4. Wakkee M, Thio HB, Prens EP, Sijbrands EJ, Neumann HA. Unfavorable cardiovascular risk profiles in untreated and treated psoriasis patients. Atherosclerosis 2007;190(1):1-9.
5. Ludwig RJ, Herzog C, Rostock A, et al. Psoriasis: a possible risk factor for development of coronary artery calcification. Br J Dermatol 2007;156(2):271-6.
6. Stern RS, Lange R. Cardiovascular disease, cancer, and cause of death in patients with psoriasis: 10 years prospective experience in a cohort of 1,380 patients. J Invest Dermatol 1988;91(3):197-201.
7. Poikolainen K, Karvonen J, Pukkala E. Excess mortality related to alcohol and smoking among hospital-treated patients with psoriasis. Arch Dermatol 1999;135(12):1490-3.
8. Mallbris L, Akre O, Granath F, et al. Increased risk for cardiovascular mortality in psoriasis inpatients but not in outpatients. Eur J Epidemiol 2004;19(3):225-30.
9. Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB. Risk of myocardial infarction in patients with psoriasis. Jama 2006;296(14):1735-41.
10. Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB, Gelfand JM. Prevalence of cardiovascular risk factors in patients with psoriasis. J Am Acad Dermatol 2006;55(5):829-35.
11. Brauchli YB, Jick SS, Curtin F, Meier CR. Association between beta-blockers, other antihypertensive drugs and psoriasis: population-based case-control study. Br J Dermatol 2008;158(6):1299-307.
12. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007;370(9596):1453-7.
13. Alevizos A, Larios G, Mariolis A. Psoriasis and risk of myocardial infarction. Jama 2007;297(4):361; author reply 2-3.
14. Wakkee M, Nijsten T. Comorbidities in dermatology. Dermatol Clin 2009;27(2):137-47, vi.
15. Conen D, Martina B, Perruchoud AP, Leimenstoll BM. High prevalence of newly detected hypertension in hospitalized patients: the value of inhospital 24-h blood pressure measurement. J Hypertens 2006;24(2):301-6.
16. Bohler S, Scharnagl H, Freisinger F, et al. Unmet needs in the diagnosis and treatment of dyslipidemia in the primary care setting in Germany. Atherosclerosis 2007;190(2):397-407.
17. de Torbal A, Boersma E, Kors JA, et al. Incidence of recognized and unrecognized myocardial infarction in men and women aged 55 and older: the Rotterdam Study. Eur Heart J 2006;27(6):729-36.
18. Naldi L, Chatenoud L, Linder D, et al. Cigarette smoking, body mass index, and stressful life events as risk factors for psoriasis: results from an Italian case-control study. J Invest Dermatol 2005;125(1):61-7.
19. Setty AR, Curhan G, Choi HK. Obesity, waist circumference, weight change, and the risk of psoriasis in women: Nurses' Health Study II. Arch Intern Med 2007;167(15):1670-5.
20. PHARMO, in Pharmo - Institute for Drug Outcomes Research. www.pharmo.nl. Last accessed march 2009.
21. Lau HS, de Boer A, Beuning KS, Porsius A. Validation of pharmacy records in drug exposure assessment. J Clin Epidemiol 1997;50(5):619-25.

22. Erkens JA, Panneman MM, Klungel OH, van den Boom G, Prescott MF, Herings RM. Differences in antihypertensive drug persistence associated with drug class and gender: a PHARMO study. Pharmacoepidemiol Drug Saf 2005;14(11):795-803.
23. WHO. WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment. Oslo, Norway: WHO; 1999.
24. WHO. WHO. International Classification of Diseases, 9th revision, clinical modification, and HIV infection codes addendum (rev. nr. 1). Geneva, Switzerland: WHO; 1987.
25. Lamberts H, Wood M, (eds). ICPC. International Classification of Primary care. Oxford: Oxford University Press; 1987.
26. Spuls PI, Bossuyt PM, van Everdingen JJ, Witkamp L, Bos JD. The development of practice guidelines for the treatment of severe plaque form psoriasis. Arch Dermatol 1998;134(12):1591-6.
27. Fry L, Baker BS. Triggering psoriasis: the role of infections and medications. Clin Dermatol 2007;25(6):606-15.
28. Brookhart MA, Patrick AR, Schneeweiss S, et al. Physician follow-up and provider continuity are associated with long-term medication adherence: a study of the dynamics of statin use. Arch Intern Med 2007;167(8):847-52.
29. Gumbs PD, Verschuren WM, Mantel-Teeuwisse AK, et al. Drug costs associated with non-adherence to cholesterol management guidelines for primary prevention of cardiovascular disease in an elderly population: the Rotterdam study. Drugs Aging 2006;23(9):733-41.
30. Stern RS, Nijsten T, Feldman SR, Margolis DJ, Rolstad T. Psoriasis is common, carries a substantial burden even when not extensive, and is associated with widespread treatment dissatisfaction. J Investig Dermatol Symp Proc 2004;9(2):136-9.
31. Nijsten T, Rolstad T, Feldman SR, Stern RS. Members of the national psoriasis foundation: more extensive disease and better informed about treatment options. Arch Dermatol 2005;141(1):19-26.
32. Cohen AD, Gilutz H, Henkin Y, et al. Psoriasis and the metabolic syndrome. Acta Derm Venereol 2007;87(6):506-9.
33. Lindegard B. Diseases associated with psoriasis in a general population of 159,200 middle-aged, urban, native Swedes. Dermatologica 1986;172(6):298-304.

Chapter 5

Psoriasis may not be an independent risk factor for acute ischemic heart disease hospitalizations: results of a large population-based dutch cohort

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Abstract

Although psoriasis has been associated with components of the metabolic syndrome, its association with myocardial infarction is less clear. A cohort study was conducted using hospital and pharmacy records of 2.5 million Dutch residents between 1997 and 2008. The risk of ischemic heart disease (IHD) hospitalizations was compared between psoriasis patients and a matched reference cohort. Additional adjustments were made for healthcare consumption and use of cardiovascular drugs. A total of 15,820 psoriasis patients and 27,577 reference subjects were included, showing an incidence rate of 611 and 559 IHD per 100,000 person-years, respectively (*P*=0.066). The age- and gender-adjusted risk of IHD was comparable between both cohorts (hazard ratio (HR)=1.10, 95% confidence interval 0.99–1.23). Before cohort entry, psoriasis patients used more antihypertensive, antidiabetic, and lipid-lowering drugs and were more often hospitalized. Adjusting for these confounders decreased the HR for IHD, but it remained comparable between both populations. There was no different risk of IHD between the subgroup of patients who only used topicals *versus* those who received systemic therapies or inpatient care for their psoriasis. This study, therefore, suggests that psoriasis is not a clinically relevant risk factor for IHD hospitalizations on the population level.

Introduction

In the past 5 years, the interest in the association between psoriasis and comorbidities, especially cardiovascular diseases, has revived.[1-6] Several observational studies found an increased risk of cardiovascular diseases. The primary underlying hypothesis is that the increased systemic inflammatory status of psoriasis patients leads to and/or aggravates other chronic (low-grade) inflammatory diseases including atherosclerosis. However, psoriasis is also associated with a considerable health-related quality of life impairment, depression, altered life styles, increased use of systemic drugs, and healthcare consumption, which may affect the relationship between psoriasis and the metabolic syndrome as well.[6, 7] Although several studies adjusted in part for potential confounders, such as diabetes, dyslipidemia, obesity, and smoking, residual confounding may be substantial.[7, 8]

More recently, psoriasis has been associated with an increased risk of myocardial infarction (MI) using the data from the UK general practice research database (GPRD).[1, 9] Another study analyzing the same cohort could not confirm an overall increased risk of MI.[10] Moreover, a Swedish population-based study found that the risk of MI was only increased in females with psoriasis, whereas another US study observed a particularly higher rate of occlusive vascular disease in male psoriasis patients.[11, 12] In the PUVA (psoralen plus ultraviolet light A) Follow-Up Study, cardiovascular mortality was comparable with the expected incidence.[13]

Although psoriasis is associated with components of the metabolic syndrome, its association with MI is still less clear. The objective of this study was therefore to conduct an exploratory study on the association between psoriasis and ischemic heart disease (IHD) by comparing the incidence of hospitalizations for IHD in psoriasis patients with controls in a large sample of the Dutch population using hospital and pharmacy-linked databases.

Results

Study population

The cohort study included 43,397 subjects of whom 15,820 (37%) had psoriasis. The mean age at cohort entry was between 48 and 49 years and 52% were female (Table 1). Psoriasis patients were significantly more likely to have been hospitalized for non-cardiovascular diseases in the 6 months before start of follow-up (7.1 *versus* 5.1%, $P<0.001$) and to have filled prescriptions for lipid-lowering, antihypertensive, and antidiabetic drugs.
Almost all patients with psoriasis had used a topical antipsoriatic therapy (99%), and 13% had used a systemic antipsoriatic therapy or were hospitalized for their psoriasis.

Table 1. Baseline characteristics of the psoriasis and reference cohort.

Variable	Psoriasis cohort	Reference cohort
No. (%)	15820 (36.5)	27577 (63.5)
Gender		
Male (%)	7583 (47.9)	13306 (48.3)
Female (%)	8237 (52.1)	14271 (51.7)
Age in years		
Mean (SD)	48.9 (16.1)	48.1 (16.1)
Prior hospitalizations[1]		
yes (%)	1130 (7.1%)*	1415 (5.1%)*
total	1676	1979
unique	1447	1802
Medical history[1]		
Lipid-lowering drugs (%)	1102 (7.0)**	1701 (6.2)**
Antihypertensive drugs (%)	3076 (19.4)***	4519 (16.4)***
Antidiabetic drugs (%)	699 (4.4)***	993 (3.6)***
Psoriasis therapies		
Topicals only	13851 (87.5)	
Systemic therapy	1969 (12.5)	
and/or hospitalization[2]		
Specific therapies ever used since start follow-up[3]:		
Topical antipsoriatic	15646 (98.9)	
Therapies[4]		
PUVA-therapy	505 (3.2)	
Methotrexate	122 (0.8)	
Ciclosporin	424 (2.7)	
Acitretin	789 (5.0)	
Fumarates	14 (0.1)	
Biologics[5]	84 (0.5)	

Abbreviations: PUVA, psoralen plus ultraviolet-A ; SD, standard deviation.
* prior hospitalizations p<0.001
** lipid-lowering drugs p=0.001
*** antihypertensive and antidiabetic drugs p<0.001
[1] in 6 months before prior to cohort entry (excluding hospitalizations for cardiovascular diseases n=100 and n=124 for the psoriasis and control cohort, respectively)
[2] Systemic drugs include PUVA therapy and hospitalization should be specific for psoriasis.
[3] Total adds up to more than 100% due to the possibility of multiple therapies per patient.
[4] coal tar, topical corticosteroids, dithranol, calcipotriol, calcitriol, tacrolimus and pimecrolimus
[5] adalimumab (n=19), efalizumab (n= 8), etanercept (n= 65), infliximab (n=2)

Event Rate and univariate analyses

The median follow-up time was about 6 years in both cohorts. In the psoriasis population, 3.7% were hospitalized for an IHD (583 events) resulting in an incidence rate of 611 IHDs (95% confidence interval (CI) 562–663) per 100,000 person-years (Table 2). In the matched cohort population, 846 IHDs occurred in 3.1% of the controls representing an incidence rate of 559 IHDs (95% CI 522–598) per 100,000 person-years. Psoriasis patients and controls had an equal likelihood of developing an IHD in time (*P*=0.066, Figure 1). The age- and gender-matched hazard ratio (HR) for IHD was borderline significantly increased for psoriasis (crude HR 1.10, 95% CI 0.99–1.23).

Acute MIs were observed 234 and 235 times per 100,000 person-years in the psoriasis and control cohort, respectively. The age- and gender-adjusted survival analysis did not show a different risk of acute MI (crude HR 0.99, 95% CI 0.84–1.17).

Multivariate survival analyses

The risk of IHD decreased but remained comparable between the psoriasis and reference cohort (adjusted HR 1.05, 95% CI 0.95–1.17, Table 2) after adjusting for the healthcare consumption

Table 2. Incidence rates of ischemic heart disease (IHD) and acute myocardial infarction (MI) in patients with psoriasis and the reference cohort, and the crude and adjusted hazard ratios (HRs).

Outcome	Events	Person years	Incidence rate[1]	95% CI	Crude HR[2]	95% CI	Adjusted HR[3]	95% CI
IHD[4]								
Ref cohort	846	151,303	559	522, 598	1		1	
Psoriasis cohort	583	95,437	611	562, 663	1.10	0.99, 1.23	1.05	0.95, 1.17
Acute MI								
Ref cohort	360	153,514	235	211, 260	1		1	
Psoriasis cohort	223	97,029	234	201, 262	0.99	0.84, 1.17	0.94	0.80, 1.11

Abbreviation: CI, confidence interval.
[1] Incidence rate per 100.000 person-years.
[2] HR adjusted for age and gender by matching.
[3] Adjusted for age, gender, prior use of antihypertensive, antidiabetic and lipid-lowering drugs, the number of prior non cardiovascular hospitalizations in 180 days prior to cohort entry and significant interaction terms.
[4] IHD includes hospitalizations for acute myocardial infarction, angina pectoris and other acute ischemic heart disease.

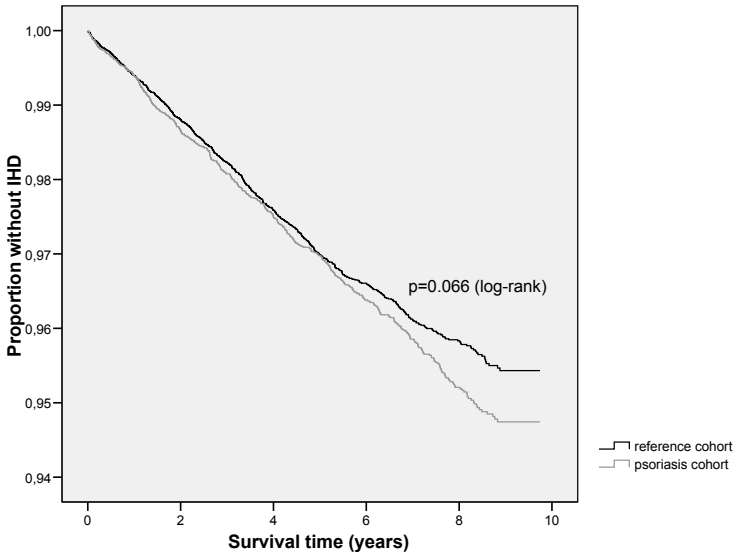

Figure 1. Crude survival for ischemic heart disease (IHD) for patients with psoriasis and the age- and gender-matched reference cohort: results of the Kaplan–Meier analysis.

proxy, metabolic drugs, and an interaction term between psoriasis and healthcare consumption. The multivariate model for MI, which did not include any significant interaction variables, showed that psoriasis was not associated with a different risk of acute MI.

Sensitivity analyses

Restricting the analysis to individuals without cardiovascular disease-associated hospitalizations in their 6 months history showed that the risk of developing an IHD remained comparable between psoriasis patients and matched references (crude HR 1.09, 95% CI 0.98–1.22).

In the cohort of psoriasis patients, those who had used PUVA, systemic antipsoriatic therapies, or were treated as in patients had no different risk of IHD than the psoriasis patients who had only used topical therapies (P=0.10).

Stratifying for age group showed that the HRs of 35,509 people of 65 years or younger and 7,888 persons older than 65 years (HR 1.06, 95% CI 0.92–1.23 and HR 1.09, 95% CI 0.93–1.28, respectively) were comparable with the HRs of the total population.

Discussion

The results of this large cohort study with valid and clinically relevant outcomes suggest that psoriasis is not a risk factor for acute IHD hospitalizations on the population level. Psoriasis patients initially seemed to have an increased risk of IHD, but after adjusting for metabolic drug use and healthcare consumption, this association seemed to be strongly affected by confounding. We observed that psoriasis patients may have a different cardiovascular risk profile for which they receive subsequent therapies, and that the risk of IHD and MI were similar to the reference population. This may seem contradictory, but it has previously been shown that there is a weak or even no association between the metabolic syndrome and the occurrence of cardiovascular events.[14] This corresponds with a prospective cohort study of mortality causes among psoriasis patients, which showed no increased cardiovascular mortality.[13]

Our data differ from the interpretations of the results of the study performed in the GPRD by Gelfland et al.[1] Despite these differences, the factual information between the GPRD-based study and our study is marginal. Their HRs for MI were 1.11 (95% CI 1.07–1.17) for mild psoriasis and 1.43 (95% CI 1.18–1.72) for severe psoriasis.[1] Moreover, another recent cohort study of the GPRD on incident psoriasis patients could not confirm previous GPRD findings and showed no overall increased risk of incident MI in psoriasis.[10] The risk of IHD tended to be increased in our study, but the analyses of our data suggest that other factors, for example, referral bias for

other disease, are important for interpretation of our results. It might well be that the results that were found in the GPRD study have been biased likewise.

On the basis of the theory that a high inflammatory state accelerates the atherosclerotic process and increases the risk of cardiovascular events, one might expect a relationship between the severity of psoriasis and the occurrence of IHD. By using the applied therapies as proxies for psoriasis severity, our data did not show a different risk of IHD between patients with more severe psoriasis (that is, systemic antipsoriatic therapies or inpatient treatments) compared with mild psoriatic patients (that is, only topicals), even after adjusting for confounders. However, using a secondary database does not allow us to draw any conclusions about the natural history of longstanding uncontrolled severe psoriasis.

We also found that psoriasis patients generally use more healthcare than "healthy" individuals. This may increase the risk of diagnosing other conditions such as cardiovascular diseases, for which additional drugs may be prescribed or patients are hospitalized.[8] MIs are, for example, asymptomatic or clinically unrecognized in 21–68% of all cases.[15, 16] As testing for interaction showed a significant interaction between psoriasis and the number of earlier hospitalizations, we reduced surveillance bias and assured a more equal comparison between cohorts by adjusting for this healthcare consumption variable. Remarkably, most other studies investigating the risk of cardiovascular events among psoriasis patients did not examine whether surveillance bias may have influenced their results. Nevertheless, this hospital- and pharmacy-based study did not have patient characteristics data such as type of psoriasis, body mass index, socioeconomic status, and life-style factors. The absence of these and other unknown risk factors for IHD may, thus, have led to overestimated risk estimates.[7]

In this large population-based cohort study, clinically relevant outcomes of cardiovascular disease based on hospital discharge diagnosis were used as end points. The PHARMO Record Linkage System collected data prospectively and irrespective of our hypothesis, which excludes recall bias. The longitudinal National Medical Register, from which the hospital data were extracted, has almost complete coverage (99%) of all hospital admissions in the Netherlands. The observed MI incidence in the reference population was comparable with that estimated by the Dutch Heart Association in the Dutch population (235 *versus* 227 per 100,000 person-years, respectively), confirming the validity of the study outcome.[17] The outcomes we studied are somewhat different from the GPRD study in which MI diagnoses were based on GP data, which may be more sensitive to misclassification basis than hospitalization records.[18]

A caveat of our study was that we based the definition of psoriasis on drug and hospitalization records, potentially resulting in misclassification, and hence, regression to the nil to show exposure-related disease. The prevalence of actively treated psoriasis patients was 0.6% (15,820

subjects). As expected, this was lower than the estimated psoriasis prevalence of 2–3% in Western populations that includes patients without prescription drugs.[19, 20] Psoriasis patients without psoriasis-specific therapies, such as vitamin-D derivatives, PUVA, or inpatient treatments, were also missed in this study. However, those subjects who had only used possible drug dispensings for psoriasis, such as corticosteroids or methotrexate, were also excluded from the reference cohort. The prevalence of more severe psoriasis was 13% in the psoriasis cohort, which is more in line with a recent estimate of 17% moderate-to-severe psoriasis in the US adults than the 3% severe psoriasis patients observed in the GPRD data set.[1, 21] However, this therapy-based classification of severity remains a proxy, as no data were available on clinical disease severity. Validation of our psoriasis definition by GP medical files has been described in detail, and showed an excellent sensitivity of 98.2% and good specificity of 80.2%.[8] Hence, we have no reason to believe that we underestimated the risk of cardiovascular disease among patients with psoriasis. A sensitivity analysis that excluded all patients with a cardiovascular event in the 6 months before cohort entry showed comparable results.

Our data showed only a slight and borderline-significant increased risk of IHD among psoriasis patients. We reason that this association resulted from residual confounding such as increased healthcare consumption. Previous studies in which psoriasis was found to be an independent risk factor for cardiovascular events may have been biased likewise. Owing to the modest positive association between psoriasis and cardiovascular diseases, correction for confounders is critical and requires prospective studies designed to address this research hypothesis. Of course, clinicians should be attentive for risk factors or internal conditions that can affect their patients' health other than their skin disease.

Materials and methods

Data source

For this study, we used data from the PHARMO Record Linkage System, which links various medical databases including those on hospital discharge information, drug dispensing, and clinical laboratory records concerning 2.5 million individuals who were or have been the residents in defined areas in the Netherlands.[22-25] The hospital records included detailed information on primary and secondary diagnoses (coded according to the International Classification of Diseases, ninth Revision[26], medical procedures, and dates of hospital admission and discharge. The drug dispensing records (coded according to the Anatomical Therapeutic Chemical Classification)[27] consisted of the dispensing date, amount dispensed, and prescription dose regimens and length.

Study population

Patients with psoriasis were identified from the Pharmo Record Linkage System database using a five-step algorithm that focused on maximizing case sensitivity based on hospitalizations and drug dispensing records. This algorithm categorized individuals according to the likelihood of having been diagnosed with psoriasis (none, possible, probable, or definite), from which only those who definitely had psoriasis were selected. In the algorithm, individuals with a hospital discharge diagnosis of psoriasis and/or psoriatic arthritis, dispensings for psoralen, calcipotriol, calcitriol or dithranol, fumaric acid, and/or efalizumab were considered as definite psoriasis patients. Patients were classified as possibly or probably having psoriasis if they did not meet any of the abovementioned criteria, but had prescriptions for topical corticosteroids, coal tar, systemic glucocorticosteroids, retinoids, methotrexate, ciclosporin, adalimumab, etanercept, and/or infliximab. UV-B was not assessed, because this therapy is administered without pharmacy prescription. In the last step of the algorithm, identified definite psoriasis patients were excluded if they had been hospitalized for skin conditions other than psoriasis, had <6 months of history before start of follow-up (which is twice the maximum prescription time allowed in the Netherlands), and/or were <18 years of age at index date. Patients were also excluded if they had a history of diseases that could, theoretically, affect the development of psoriasis or its severity (that is, HIV, immune disorders, inflammatory bowel diseases, hepatitis B and C, multiple sclerosis, rheumatoid arthritis, and status after organ transplant).

From the pool of people with no likelihood of having psoriasis, reference subjects were selected and matched in a 1:2 ratio for age, gender, and presence of a database record within 30 days of cohort entry of a definite psoriasis patient. Similar to the psoriasis patients, reference subjects were excluded if <6 months of history was available or if they were hospitalized for dermatological diseases or the conditions listed above.

Follow-up period

Patients with psoriasis were followed from the first available date of an active treatment or hospitalization for psoriasis between 1998 and 2007. Subjects in the comparison cohort were followed from random drug dispensing or hospitalization occurring within 30 days of the start of follow-up of their matched psoriasis patient. For all subjects, follow-up time ended with the last drug dispensing available before 2008, an IHD, or death, whichever came first.

Study outcomes

The primary study outcome was hospitalization for acute IHD (that is, acute MI, other acute IHD, and angina pectoris). In addition, acute MI was studied separately.

Potential confounders

For each subject, we explored dispensings of antihypertensives, lipid-lowering, and antidiabetic drugs in 6 months before cohort entry to provide a proxy for the presence of treated dyslipidemia, hypertension, and diabetes mellitus. To adjust for healthcare utilization, we calculated the total number of hospitalizations (except for cardiovascular diseases to avoid overadjustment) in 6 months before cohort entry.[28] No information was available on life-style factors such as physical exercise, diet, smoking, alcohol consumption, or health-related quality of life.

Statistical analysis

Continuous variables are presented as means (standard deviations) or median (interquartile range) and were tested for statistically significant differences using the Student's *t*-test and the Mann–Whitney test, respectively. Incidence rates and 95% CIs, which were calculated using Byar's approximation[29], are presented as events per 100,000 person-years. Kaplan–Meier, and univariate and multivariate Cox proportional hazard analyses were performed to compare the likelihood of registrating the study outcome between the two cohorts. Owing to age and gender matching, the "crude" HRs already take into account these potential confounders. Biologically plausible and available confounding variables such as antihypertensives, antidiabetic and lipid-lowering drug use, and number of hospitalizations in 180 days before cohort entry, all changed the HR for psoriasis by 10% or more in the bivariate analyses and were therefore included in the multivariate model.[30] In the multivariate model, these confounders were also tested for interaction with psoriasis. Visual inspection of the log(-log) survival plots against time that confirmed the proportional hazard assumptions were met.

Several sensitivity analyses were performed. First, the analyses were restricted to patients without a cardiovascular event in the 6 months before cohort entry to increase the likelihood of examining incident events. Effect modification by age on the risk estimates was explored by stratification for age (≤65 and >65 years) and by testing for interaction with psoriasis. Subgroup survival analyses were conducted to analyse whether there was a different risk of IHD between psoriasis patients who only used topical therapies *versus* those who used PUVA, systemic antipsoriatic drugs, and/or were hospitalized. All statistical tests were two-sided and a *P*-value <0.05 was considered statistically significant. The analyses were performed using SPSS 15.0 (SPSS, Chicago, IL). Adherence to the STROBE (The Strengthening the Reporting of Observational Studies in Epidemiology) guidelines, especially for the multivariate analysis, assured the reporting of this observational study.[30]

References

1. Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB. Risk of myocardial infarction in patients with psoriasis. Jama 2006;296(14):1735-41.
2. Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB, Gelfand JM. Prevalence of cardiovascular risk factors in patients with psoriasis. J Am Acad Dermatol 2006;55(5):829-35.
3. Cohen AD, Gilutz H, Henkin Y, et al. Psoriasis and the metabolic syndrome. Acta Derm Venereol 2007;87(6):506-9.
4. Wakkee M, Thio HB, Prens EP, Sijbrands EJ, Neumann HA. Unfavorable cardiovascular risk profiles in untreated and treated psoriasis patients. Atherosclerosis 2007;190(1):1-9.
5. Kimball AB, Gladman D, Gelfand JM, et al. National Psoriasis Foundation clinical consensus on psoriasis comorbidities and recommendations for screening. J Am Acad Dermatol 2008;58(6):1031-42.
6. Wakkee M, Nijsten T. Comorbidities in dermatology. Dermatol Clin 2009;27(2):137-47, vi.
7. Nijsten T, Wakkee M. Complexity of the association between psoriasis and comorbidities. J Invest Dermatol 2009;129.
8. Wakkee M, Meijer W, Neumann HA, Herings RM, Nijsten T. Psoriasis may not be an independent predictor for the use of cardiovascular and anti-diabetic drugs: a 5-year prevalence study. Acta Derm Venereol 2009;89(5):476-83.
9. Kaye JA, Li L, Jick SS. Incidence of risk factors for myocardial infarction and other vascular diseases in patients with psoriasis. Br J Dermatol 2008;159(4):895-902.
10. Brauchli YB, Jick SS, Miret M, Meier CR. Psoriasis and risk of incident myocardial infarction, stroke or transient ischaemic attack: an inception cohort study with a nested case-control analysis. Br J Dermatol 2009.
11. McDonald CJ, Calabresi P. Occlusive vascular disease in psoriatic patients. N Engl J Med 1973;288(17):912.
12. Lindegard B. Diseases associated with psoriasis in a general population of 159,200 middle-aged, urban, native Swedes. Dermatologica 1986;172(6):298-304.
13. Stern RS, Lange R. Cardiovascular disease, cancer, and cause of death in patients with psoriasis: 10 years prospective experience in a cohort of 1,380 patients. J Invest Dermatol 1988;91(3):197-201.
14. Sattar N, McConnachie A, Shaper AG, et al. Can metabolic syndrome usefully predict cardiovascular disease and diabetes? Outcome data from two prospective studies. Lancet 2008;371(9628):1927-35.
15. Aronow WS. Silent MI. Prevalence and prognosis in older patients diagnosed by routine electrocardiograms. Geriatrics 2003;58(1):24-6, 36-8, 40.
16. de Torbal A, Boersma E, Kors JA, et al. Incidence of recognized and unrecognized myocardial infarction in men and women aged 55 and older: the Rotterdam Study. Eur Heart J 2006;27(6):729-36.
17. Dutch Heart Association Nederlandse Hartstichting. http://www.hartstichting.nl (File Hart-en vaatziekton in Nederland 2005). Accessed18 September 2009.
18. Hammad TA, McAdams MA, Feight A, Iyasu S, Dal Pan GJ. Determining the predictive value of Read/OXMIS codes to identify incident acute myocardial infarction in the General Practice Research Database. Pharmacoepidemiol Drug Saf 2008;17(12):1197-201.
19. Stern RS, Nijsten T, Feldman SR, Margolis DJ, Rolstad T. Psoriasis is common, carries a substantial burden even when not extensive, and is associated with widespread treatment dissatisfaction. J Investig Dermatol Symp Proc 2004;9(2):136-9.
20. Nijsten T, Rolstad T, Feldman SR, Stern RS. Members of the national psoriasis foundation: more extensive disease and better informed about treatment options. Arch Dermatol 2005;141(1):19-26.

21. Kurd SK, Gelfand JM. The prevalence of previously diagnosed and undiagnosed psoriasis in US adults: results from NHANES 2003-2004. J Am Acad Dermatol 2009;60(2):218-24.
22. Lau HS, de Boer A, Beuning KS, Porsius A. Validation of pharmacy records in drug exposure assessment. J Clin Epidemiol 1997;50(5):619-25.
23. Herings RM, Urquhart J, Leufkens HG. Venous thromboembolism among new users of different oral contraceptives. Lancet 1999;354(9173):127-8.
24. Erkens JA, Panneman MM, Klungel OH, van den Boom G, Prescott MF, Herings RM. Differences in antihypertensive drug persistence associated with drug class and gender: a PHARMO study. Pharmacoepidemiol Drug Saf 2005;14(11):795-803.
25. Pharmo (http://www.pharmo.nl). (Accessed on 10 January 2009)
26. WHO International Classification of Diseases, 9th revision, clinical modification, and HIV infection codes addendum (rev. nr. 1). Geneva, Switzerland: WHO; 1987.
27. WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment. Oslo, Norway: WHO; 1999.
28. Smitten AL, Choi HK, Hochberg MC, et al. The risk of hospitalized infection in patients with rheumatoid arthritis. J Rheumatol 2008;35(3):387-93.
29. Breslow NE, Day NE. Statistical methods in cancer research. Volume II--The design and analysis of cohort studies. IARC Sci Publ 1987(82):1-406.
30. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007;370(9596):1453-7.

Chapter 6

Increased risk of serious infections in psoriasis patients: a population based cohort

M. Wakkee
E. de Vries
P. van den Haak
T. Nijsten

Submitted

Abstract

Background Immunological alterations due to psoriasis and/or its therapies may affect the risk of serious infections.

Objective We explored the psoriasis patients' baseline and therapy-related risk of contracting an infectious disease (ID) requiring hospitalization in a large population based cohort.

Methods The incidence of IDs were compared between psoriasis patients and a randomly selected cohort (ratio 1:5) using hospital and pharmacy databases covering 2.5 million Dutch residents between 1997-2008. First and multiple IDs were defined and categorized into 20 groups based on primary ICD-9 discharge diagnoses. Multivariate Cox regression and Poisson event-count models were used to test the risk difference of IDs between psoriasis patients and reference cohort.

Results A total of 25,742 psoriasis patients and 128,710 reference subjects were followed for approximately 6 years. The likelihood of IDs in psoriasis patients was twice as high as the reference population (908 versus 438 events per 100,000 person-years, crude hazard ratio (HR)=2.08 (95% confidence interval [CI] 1.96-2.22)). In a multivariate model the HR decreased to 1.54 (95%CI 1.44-1.65). This risk was highest for more severe psoriasis patients (adjusted HR=1.81, 95%CI1.57-2.08), but was not associated with recent systemic anti-psoriatic drug dispensings. Respiratory tract, abdominal and skin infections occurred most frequently in psoriasis patients. Multiple event analysis that counted the total number of infectious discharge diagnoses gave similar results.

Limitations No data were available on lifestyle factors.

Conclusion The risk of severe infections was significantly higher for psoriasis patients compared to controls and could not be explained by exposure to systemic anti-psoriatic drugs.

Introduction

Psoriasis patients may have an increased risk of serious infections due to intrinsic immunological disturbances associated with psoriasis itself. This risk may be affected as well by immunomodulatory anti-psoriatic drugs including biologicals, which are being widely adopted for the treatment of moderate to severe psoriasis, the presence of other comorbidities and/or unhealthy lifestyle factors. However, investigating such a multifactorial association is complex.[1] Up until now, few studies have examined the risk of serious infections in patients with psoriasis.

Basic research has demonstrated that there is a higher expression of innate immunity genes in lesional psoriasis skin which enhances its epidermal host defense.[2-4] Similarly, in a large clinical study psoriasis inpatients with an early onset of their disease also had lower risks of bacterial and viral skin infections than other dermatological inpatients.[5] The risk of certain systemic infections in patients with psoriasis may thus be reduced by the increased epidermal barrier function.

On the contrary, one population-based study that investigated diseases associated with psoriasis suggested that these patients may have an increased risk of pneumonia and systemic viral infections.[6] A case series of patients with erythrodermic psoriasis also reported a possible higher risk of staphylococcal septicaemia.[7]

Despite the relevance of the risk of infections in patients with psoriasis, especially with the current immunomodulatory therapies, insufficient data are available on the baseline and drug-associated risk of infections. We therefore determined whether patients with psoriasis have a different baseline risk of infections that require hospitalization compared to subjects without psoriasis. We also wanted to establish whether the risk of serious infections is affected by anti-psoriatic therapies.

Methods

Data source

For this study we used data from the PHARMO Record Linkage System, which links various medical databases, including the National Medical Register of hospital discharge information and outpatient drug dispensing records (by general practitioners and medical specialists) concerning 2.5 million individuals who were ever residents in defined areas in the Netherlands.[8-12] The hospital records included detailed information on primary and secondary diagnoses (coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification[13]),

medical procedures, and dates of hospital admission and discharge. The drug dispensing records (coded according to the Anatomical Therapeutic Chemical Classification[14]) consisted of the dispensing date, amount dispensed, prescribed dose regimens, and prescription length.

Study population

Patients with psoriasis were identified from the PHARMO Record Linkage System database by an algorithm which focused on maximizing case sensitivity on the basis of hospitalizations and drug dispensing records. Previous validation of this algorithm using the presence of a psoriasis diagnosis in the GPs' medical files showed a sensitivity of 98.2% and specificity of 80.2%.[15] The algorithm categorizes individuals according to the likelihood of having been diagnosed with psoriasis (none, possible, probable or definite). In the algorithm, individuals were considered as definitely having psoriasis if they had a hospital discharge diagnosis of psoriasis and/or psoriatic arthritis, and/or dispensings for psoralen, calcipotriol, calcitrol, ditranol, fumaric acid or efalizumab. Patients were classified as possibly or probably having psoriasis if they did not meet any of these criteria, but had dispensing records for topical corticosteroids, coal tar, systemic glucocorticosteroids (although this is not considered standard therapy according the Dutch psoriasis guidelines[16]), retinoids, methotrexate, ciclosporin, adalimumab, etanercept and/or infliximab. Ultraviolet-B could not be assessed because this therapy is administered without pharmacy prescription. The study was restricted to subjects identified as having definite psoriasis and excluded possible and probable psoriasis patients. In the last step of the algorithm, identified definite psoriasis patients were excluded if they had been hospitalized for non-infectious skin conditions other than psoriasis and/or had less than 6 months of available history at cohort entry date. In the absence of clinical psoriasis severity measures, patients were categorized into mild psoriasis (i.e. using only topical therapies) or severe psoriasis (i.e. patients who had had psoralen with ultraviolet-A [PUVA]-therapy, systemic therapies and/or inpatient treatment for their psoriasis).[17]

For every psoriasis patient included, five reference subjects were randomly selected from the pool of people with no likelihood of having psoriasis. Like the psoriasis patients, reference subjects were excluded if <6 months of history was available before the cohort entry date of the matched psoriasis patient, or if they had a history of hospitalizations for dermatological diseases or the conditions listed above.

Follow-up period

Patients with psoriasis were followed from the first available date of an active treatment or hospitalization for psoriasis between 1998-2007. Subjects in the reference cohort were followed

from a random date during their available follow-up, but to assure equal distribution of cohort entry dates, the cohorts were frequency matched for the year of cohort entry date. For the survival analyses follow-up time ended with the investigated ID hospitalization, death or year of last available prescription or random hospitalization, whichever came first. For the multiple event analyses follow-up time ended with death or in the year of the last available prescription or hospitalization, whichever came first.

Study outcomes

The primary study outcomes were the incidence rates of first and multiple serious infections defined as those infections requiring hospitalization. The infections were classified according to ICD-9-CM codes and arranged into 20 groups of related infections on the basis of a classification by Simonsen et al, which demonstrated to comprise 93% of all infectious disease discharge diagnoses.[18] We added a group of 'viral diseases accompanied by exanthem' (ICD-9-CM 050-059), modified 'infections of skin and subcutaneous tissue' by including erysipelas, excluded 'selected perinatal infections', and extended 'hospitalization for tuberculosis' with drug prescriptions specific for active tuberculosis, since almost all Dutch patients with tuberculosis are treated in outpatient settings.
As a secondary outcome, we investigated whether the risk of serious infections in the cohort of psoriasis patients was affected by systemic anti-psoriatic therapies.

Potential confounders

Besides age at cohort entry (continuous) and gender, we included the total number of non-infectious hospitalizations within 6 months before cohort entry date as a proxy-variable for the presence of comorbidities.[19] Since both diabetes mellitus and COPD or asthma are known predictors for the occurrence of infections[20-22], we also included prescriptions for anti-diabetic drugs as well as for COPD and anti-asthmatic drugs as dichotomous surrogate variables for these diseases. Hospitalization for inflammatory bowel disease was examined as a confounder for relevant ID subgroups such as abdominal and rectal infections, enteric infections and hepatobiliary disease. No information was available on life-style factors such as smoking, alcohol consumption and diet.

Statistical analysis

We used the Chi-square test to compare categorical variables and Student's t-test to compare continuous variables. Incidence rates were presented as events per 100,000 person-years, and Kaplan-Meier and Cox proportional hazard models were used to compare the incidence of first ID hospitalizations (including also specific drug dispensing for tuberculosis) between the

psoriasis and reference cohort. Using two models, the hazard ratio (HR) and 95% confidence interval (CI) were subsequently adjusted for confounding. In the first model we adjusted for all biologically plausible and available confounders referred to above, including the a priori hypothesized interaction between psoriasis x age. In the second model we adjusted for all biological plausible and available confounders that changed the HR for psoriasis by 10% or more in the bivariate analysis.[23] A log-rank trend test and comparable multivariate analyses were conducted to investigate whether there was a different risk of IDs between psoriasis patients who only used topical therapies and those who used PUVA, systemic antipsoriatic drugs and/or were treated as psoriasis inpatients. Visual inspection of the log(-log) survival plots against time confirmed the proportional hazard assumptions were met. Adjusted attributable risks were calculated by multiplying the hazard ratios adjusted for substantial confounders by the difference between the incidence rate in the psoriasis cohort and the reference cohort. The inverse of the attributable risk was used to determine the excess risk.

We also used Poisson regression models to explore the risk difference between the two cohorts when all unique ID hospitalizations were included. To adjust the incidence rate ratios (IRR) for potential confounders, the two models described above were also applied to the multivariate Poisson regression models. The goodness-of-fit test showed that the Poisson model was adequate (p=1.00).

All individual ID groups were evaluated using proportional hazard models. To prevent overfitted models, only ID groups with frequencies ≥50 were investigated using the full model.[24] A subgroup survival analysis in the cohort of more severe psoriasis patients was conducted to analyse whether the use of a systemic anti-psoriatic therapy within 90 days prior to an event was an independent predictor for IDs.

Several sensitivity analyses were performed. First, the analyses were restricted to subjects who had not received inpatient treatment for an ID in the 6 months prior to cohort entry date because these subjects may have a higher risk of IDs. In a second analysis, we excluded subjects with a concomitant disease that may be associated to psoriasis and the risk of IDs such as rheumatoid arthritis, immune disorders, inflammatory bowel disease, hepatitis B and C; we also excluded those who had used HAART therapy during their follow-up, or oral corticosteroids less than 90 days before an ID. All statistical tests were two-sided, and a p-value <0.05 was considered statistically significant. The analyses were performed using SPSS 15.0 (SPSS Inc. Chicago, IL), except for the Poisson regression analysis, which was performed with Stata 9.0 (StataCorp., College Station, Texas). Adherence to the STROBE guidelines, especially for the multivariate analysis, assured the reporting of this observational study.[23]

Results

Study population

A total of 154,452 people, 25,742 (16.7%) of whom had psoriasis, were followed for an average of six years (Table 1). Patients with psoriasis were older than the reference cohort (mean age 44.3 versus 38.2 years, p<0.001), but the distribution between males and females was comparable. The proportion of subjects with a hospitalization of any kind in the six months prior to cohort entry was almost twice as high in the psoriasis cohort. During the available follow-up, 8.4% of the psoriasis patients were prescribed an anti-diabetic drug, against 3.1% of the reference subjects. COPD or asthmatic drugs were prescribed twice as often in the psoriasis cohort (22.7%) as in the reference cohort (10.4%). Almost all patients with psoriasis were treated with a topical antipsoriatic therapy (98%) of which calcitriol or calcipotriol being the most frequently prescribed (87%). In the psoriasis cohort, 689 people (2.7%) were treated with PUVA, 1817 (7.1%) used a systemic therapy, and 899 (3.5%) had an inpatient treatment for psoriasis during their follow-up. Acitretin was the most commonly prescribed systemic therapy (4.3%), followed by PUVA-therapy (2.7%) and ciclosporin (2.5%).

Table 1. Baseline characteristics of the psoriasis and reference cohort

Variable	Psoriasis cohort	Reference cohort	P value
No.	25,742 (16.7%)	128,710 (83.3%)	
Gender			
Male	12,517 (48.6%)	62,199 (48.3%)	0.38
Female	13,225 (51.4%)	66,511 (51.7%)	
Age (y) at cohort entry			
Mean (SD)	44.3 (19.6)	38.2 (22.9)	<0.001
Years of follow-up			
Sum	164,455	789,103	
Mean (SD)	6.39 (2.90)	6.13 (2.96)	<0.001
Prior hospitalizations[1]	1840 (7.1%)	5065 (3.9%)	
Infectious (%)	116 (0.4%)	423 (0.3%)	
Non-infectious (%)	1762 (6.8%)	4745 (3.7%)	<0.001
Anti-diabetic drugs[1] (%)	2154 (8.4%)	4022 (3.1%)	<0.001
Drugs used in asthma and COPD[1] (%)			
	5834 (22.7%)	13,379 (10.4%)	<0.001
Inflammatory bowel disease (%)[2]	75 (0.3)	115 (0.1)	<0.001

COPD: chronic obstructive pulmonary disease, SD: standard deviation

[1] Number and percentage of subjects in cohort.

[2] Based on hospitalization records.

Risk of an infectious disease hospitalization

In the psoriasis cohort 1,447 people were at least hospitalized once for an ID (incidence of first IDs=908 IDs per 100,000 person-years). In the reference cohort 3,402 subjects had at least one

ID, which represents an incidence rate of 438. The likelihood of a first ID was two times higher in the psoriasis cohort than in the reference cohort (crude HR 2.1, 95%CI 2.0-2.2) (Table 2). After adjustment for all available and biologically plausible confounders including age, gender, number of prior hospitalizations, COPD/anti-asthmatic drugs, antidiabetic drugs and an interaction term between psoriasis and age, the risk remained significant but decreased to 1.8 (95%CI 1.5-2.0) (Table 2). In the second model that only included substantial confounders, which were prescriptions for diabetic and COPD/anti-asthmatic drugs, the adjusted HR decreased even more (adjusted HR 1.6, 95% CI 1.9-2.2) (Table 2).

Table 2. Incidence of first infectious diseases (ID) requiring hospitalizations in the psoriasis and reference cohort[1]

	Reference cohort (n=128,710)	Psoriasis cohort (n=25,742)	Psoriasis cohort using topicals only (n=22,709)	Psoriasis cohort using PUVA, systemic drugs and/or inpatient treatment (n=3033)
No. of patients with an ID	3402	1447	1217	230
No. of person-years	777,545	159,335	138,651	20,685
Rate of first ID[2]	437.5	908.1	877.7	1111.9
Crude HR (95%CI)	1	2.08 (1.96-2.22)	2.01 (1.88-2.15)	2.53 (2.21-2.90)
Adjusted HR for full model[3] (95%CI)	1	1.75 (1.50-2.04)	1.71 (1.47-2.00)	2.02 (1.66-2.46)
Adjusted HR for substantial confounders (95%CI)[4]	1	1.58 (1.48-1.68)	1.54 (1.44-1.65)	1.81 (1.57-2.08)
Adjusted attributable risk for substantial confounders[2]	NA	743	678	1220
Excess risk	NA	1 ID per 135 patients per year	1 ID per 148 patients per year	1 ID per 82 patients per year

HR: hazard ratio, CI: confidence interval.

[1] Survival analyses only include the first ID hospitalization.

[2] Per 100,000 person-years.

[3] Adjusted for age, gender, number of prior hospitalizations, COPD/anti-asthmatic drugs, antidiabetic drugs, psoriasis x age.

[4] If a confounder changed the risk of the psoriasis population by ≥10%, it was considered substantial confounder. In all analyses the following substantial confounders were included: COPD/asthmatic drugs and antidiabetic drugs.

The crude survival until a first ID showed a significant trend, patients with severe psoriasis having the highest likelihood of IDs, followed by mild psoriasis patients and the reference cohort ($p<0.001$ log-rank, Figure 1). After adjustment for substantial confounders, both subgroups retained a significantly higher risk for an ID than the reference cohort (Table 2). This resulted in an excess risk of one ID per 135 psoriasis patients per year after adjustment for substantial confounders and one additional ID per 148 mild and 82 severe psoriasis patients.

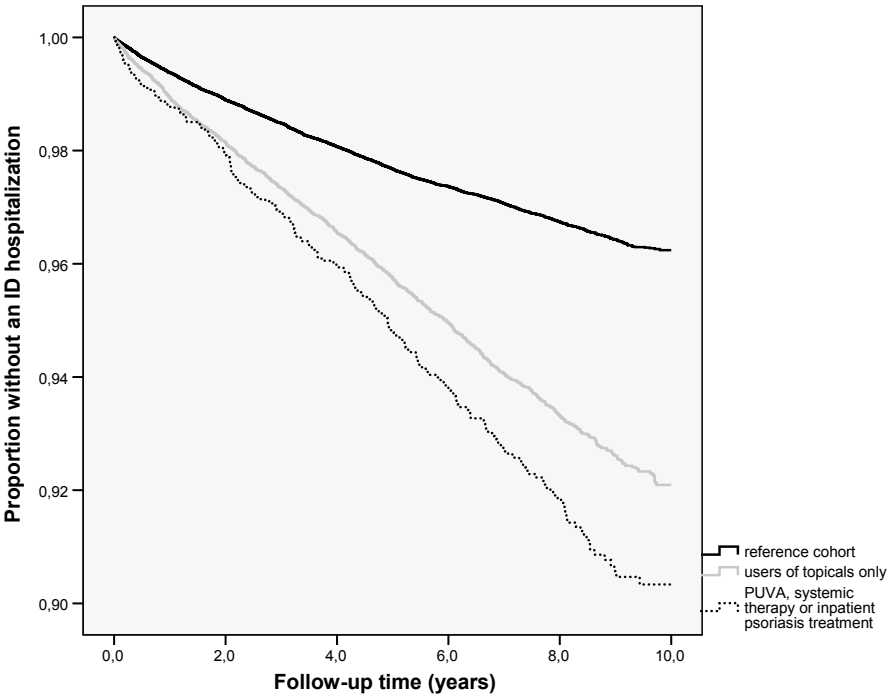

Figure 1. Crude survival of ID hospitalizations for patients with psoriasis according to the therapy applied and the reference cohort: results of the Kaplan-Meier analysis.

Risk of multiple infectious disease hospitalizations

In the psoriasis cohort 1,447 people had a total of 1,793 IDs, which is equal to an incidence rate of 1,090 infections per 100,000 person-years. In the reference cohort, 3,402 people had a total of 4,019 IDs, which is equal to an incidence rate of 509. In the univariate analysis, the risk of an ID was subsequently twice as high in the psoriasis cohort (crude IRR 2.1, 95% CI 2.0-2.3). The likelihood of multiple IDs was significantly higher for patients with severe psoriasis than for those with mild psoriasis (p=0.01). Among severe psoriasis patients the likelihood of multiple IDs was even 2.5 times higher than in the reference population Other substantial predictors for multiple IDs were the use of anti-diabetic drugs and COPD/anti-asthmatic drugs (crude IRR=3.4, 95% CI 3.1-3.7 and crude IRR=4.0, 95% CI 3.8-4.2, respectively, Table 3). In both multivariate models presented in Table 3, psoriasis remained a significant predictor for multiple IDs, with ratios comparable to those of first IDs only (Table 2).

Drug induced risk of infectious disease hospitalizations

Thirty-nine of the 1,793 infections in the psoriasis cohort had been preceded by a recently filled prescription (<90 days prior to an ID) for a systemic anti-psoriatic drug, and 16 by inpatient

Table 3. Univariate and multivariate analysis of potential predictors of hospitalizations for infectious diseases.

	Univariate IRR (95% CI)	Multivariate IRR for the full model[1] (95% CI)	Multivariate IRR with substantial confounders (95% CI)[2]
Age (y)	1.0085 (1.007-1.010)	1.007 (1.004-1.011)	-
Gender			
Male	1	1	-
Female	0.89 (0.84-0.93)	0.87 (0.83-0.92)	-
Psoriasis			
No	1	1	1
Topicals only	2.08 (1.96-2.21)	1.73 (1.50-1.99)	1.54 (1.45-1.64)
Systemic therapies or hospitalizations	2.54 (2.25-2.87)	1.97 (1.65-2.35)	1.74 (1.54-1.96)
Prior hospitalizations(no.)	1.22 (1.21-1.24)	1.16 (1.15-1.18)	-
Anti-diabetic drugs			
Yes	3.37 (3.11-3.65)	2.12 (1.95-2.31)	2.31 (2.13-2.50)
COPD/asthmatic drugs			
Yes	3.95 (3.75-4.17)	3.34 (3.16-3.53)	3.38 (3.20-2.57)
Psoriasis x age	1.00 (1.00-1.00)	0.997 (0.993-0.9995)	-

IRR: incidence rate ratio, CI: confidence interval, COPD: chronic obstructive pulmonary disease.

[1] Adjusted for age, gender, number of prior hospitalizations, COPD/anti-asthmatic drugs, antidiabetic drugs, psoriasis x age.

[2] If a confounder changed the IRR of the psoriasis population with ≥10%, it was considered substantial confounder.

treatment for psoriasis. Specification per systemic anti-psoriatic drug showed that the proportion of users who had had an ID within 90 days of receiving a prescription was 0.4% (3 of 689 users) for PUVA-therapy, 1.1% (2 of 174 users) for methotrexate, 1.2% (1 of 81 users) for fumarates, 1.3% for acitretin (14 of 1103 users) and 1.7% (11 of 640 users) for ciclosporin. Biologicals were used by 120 patients, three of whom (2 adalimumab users, 1 etanercept user) had had an ID within 90 days of receiving their prescription.

The use of these systemic anti-psoriatic therapies less than 90 days prior to an ID was not a significant predictor for an ID in the cohort of severe psoriasis patients (crude HR=1.1, 95% CI 0.7-1.6). neither after adjusing for confounders (adjusted HR = 1,0, 95% CI 0,7-1,6). Further analyses per systemic anti-psoriatic drug were not possible due to the very small proportions of IDs per subgroup.

Risks in various infectious disease subgroups

Except for meningitis, the incidence rates in all ID subgroups, were higher in the psoriasis population than in the reference population (Table 4). The most frequent primary hospital discharge diagnoses of IDs were lower and upper respiratory tract infections (incidence rate of 220 and 215, respectively). Other IDs with an incidence rate of approximately 100 were abdominal and

Table 4. Incidence rates and hazard ratios of hospitalizations for various infectious disease (ID) groups[a].

ID group	Incidence psoriasis cohort (n=25,742)		Incidence rate reference cohort (n=128,710)		Crude HR (95% CI)	HR adjusted for the full model (95% CI)[2]	HR adjusted for substantial confounders (95% CI)[3]	Included confounders
	Nr.	Rate[1]	Nr.	Rate[1]				
Lower respiratory tract infections	360	220.4	738	93.7	2.37 (2.09-2.68)	1.20 (1.05-1.37)	1.22 (1.07-1.39)	*Age, anti-diabetic drugs and COPD/ asthmatic drugs*
Upper respiratory tract infections	351	215.2	1045	133.2	1.63 (1.44-1.84)	1.83 (1.61-2.07)	1.86 (1.64-2.11)	*Age, COPD/asthmatic drugs*
Abdominal and rectal infections	183	111.8	521	66.2	1.69 (1.43-2.01)	1.82 (1.53-2.16)	1.88 (1.59-2.24)	*Age*
Cellulites and erysipelas	181	110.5	290	36.8	3.01 (2.50-3.63)	1.80 (1.19-2.73)	2.71 (2.24-3.27)	*Anti-diabetic drugs*
Kidney, urinary tract and bladder infections	139	84.7	256	32.5	2.61 (2.12-3.20)	1.90 (1.54-2.35)	1.92 (1.56-2.37)	*Age, anti-diabetic drugs*
Postoperative infections	88	53.6	139	17.6	3.05 (2.33-3.98)	2.48 (1.89-3.26)	2.53 (1.92-3.32)	*Age, anti-diabetic drugs*
Infection and inflammatory reaction to prosthetic devices	46	28.0	92	11.7	2.41 (1.69-3.44)	1.93 (1.35-2.77)	1.98 (1.38-2.84)	*Age, anti-diabetic drugs*
Septicemia	45	27.4	71	9.0	3.05 (2.10-4.43)	2.18 (1.48-3.20)	2.24 (1.52-3.29)	*Age, anti-diabetic drugs*
Enteric infections	33	20.1	80	10.1	1.99 (1.33-2.98)	1.75 (1.15-2.66)	1.79 (1.19-2.71)	*Anti-diabetic drugs*
Hepatobiliary disease	24	14.6	34	4.3	3.40 (2.02-5.73)	2.64 (1.55-4.50)	2.85 (1.68-4.84)	*Age, anti-diabetic drugs*
Viral diseases accompanied by exanthema	23	14.0	27	3.4	4.13 (2.37-7.20)	3.44 (1.96-6.06)	3.63 (2.08-6.34)	*Age*

Table 4 continued

ID group	Incidence psoriasis cohort (n=25,742)		Incidence rate reference cohort (n=128,710)		Crude HR (95% CI)	HR adjusted for the full model (95% CI)[2]	HR adjusted for substantial confounders (95% CI)[3]	Included confounders
	Nr.	Rate[1]	Nr.	Rate[1]				
Pelvic inflammatory disease	16	9.7	51	6.5	1.50 (0.86-2.63)	1.61 (0.91-2.85)	1.50 (0.86-2.63)	*None*
Osteomyelitis	16	9.7	37	4.7	2.09 (1.16-3.76)	1.28 (0.70-2.35)	1.32 (0.72-2.41)	*Age, anti-diabetic drugs*
Infections in pregnancy	12	7.3	30	3.8	1.91 (0.98-3.74)	-	2.61 (1.32-5.17)	*Age*
Tuberculosis[4]	11	6.7	39	4.9	1.38 (0.70-2.69)	1.18 (0.60-2.34)	1.19 (0.60-2.35)	*Age, prior hosp, anti-diabetic drugs*
Infections of the heart	9	5.5	18	2.3	2.42 (1.09-5.38)	-	2.00 (0.89-4.50)	*Age, anti-diabetic drugs*
Oral infections	9	5.5	11	1.4	3.99 (1.65-9.62)	-	3.91 (1.56-9.82)	*Age, anti-diabetic drugs*
Viral CNS infection	7	4.3	13	1.6	2.60 (1.04-6.53)	-	3.02 (1.18-7.70)	*Age*
Mycoses	4	2.4	13	1.6	1.49 (0.49-4.57)	-	1.19 (0.38-3.71)	*Age, prior hosp*
Meningitis	3	1.8	28	3.5	0.52 (0.16-1.71)	-	0.52 (0.16-1.71)	*None*

Abbreviations: CI: confidence interval, HR: hazard ratio, ID: infectious disease.

[1] Incidence rates are presented per 100,000 person-years and include all unique ID group hospitalizations documented per person.

[2] Adjusted for age, gender, number of prior hospitalizations, anti-diabetic drugs, prescriptions for COPD/anti-asthmatic drugs (for upper and lower respiratory tract infections), inpatient treatments for inflammatory bowel disease (enteric infections, abdominal and rectal infections) if the ID group contained ≥50 events.

[3] Biologically plausible confounders were tested and added to the model if they changed the HR for psoriasis by ≥ 10%: age, gender, number of prior hospitalizations, prescriptions for anti-diabetic drugs, prescriptions for COPD/anti-asthmatic drugs (for upper and lower respiratory tract infections), inpatient treatments for inflammatory bowel disease (enteric infections, abdominal and rectal infections).

[4] TB is recorded based on inpatient treatments and outpatient prescriptions for active TB.

rectal infections, cellulites and erysipelas, and kidney and urinary tract infections. After adjustment for substantial confounders, the risk of these frequently occuring ID groups remained significantly higher for psoriasis patients, ranging between 1.2 for lower respiratory tract infections and 2.7 for cellulites and erysipelas. Other ID groups with incidence rates of at least 10 and with psoriasis patients having at least a 2.5 times higher adjusted risk than the reference population were viral diseases accompanied by exanthema, hepatobiliary disease, and postoperative infections.

Sensitivity analyses

The sensitivity analysis that excluded subjects who had been hospitalized for IDs less than six months before cohort entry (n=539) produced comparable crude and adjusted hazard ratios (adjusted HR=1.6, 95% CI 1.5-1.7). The hazard ratio also remained identical after the exclusion of 331 psoriasis patients and 441 reference subjects with previously described possible confounding factors (e.g. rheumatoid arthritis, HAART-therapy and oral corticosteroids, adjusted HR=1.6, 95% CI 1.5-1.7).

Discussion

The results of this large population-based cohort study indicate that the risk of serious infections requiring hospitalization is about two times higher in psoriasis patients than in the general Dutch population. The ID risk was positively related to the psoriasis severity. It was highest in subjects with more severe psoriasis (i.e. those who had used PUVA, a systemic therapy or an inpatient treatment) showing one additional ID per 82 severe psoriasis patients, while there was one extra ID per 148 mild psoriasis cases. The occurrence of IDs was substantially confounded by comorbidities such as diabetes and obstructive pulmonary diseases partly explaining the difference between the psoriasis and reference cohort. Based on possible immunosuppressive effects of systemic therapies like methotrexate, ciclosporin, acitretin, fumarates or a biological therapy one may expect a possible association with IDs. However, only 2.0% of all 1,793 IDs were preceded by a recent systemic drug dispensing and we were not able to confirm an association with IDs in the psoriasis cohort.

This is the largest population based study to have investigated all major IDs requiring hospitalization in psoriasis patients. Not only did we find no evidence that an increased epidermal host defence in psoriasis had a protective effect of serious infections, we even observed significantly more hospitalizations for skin infections such as cellulites and erysipelas. Previous studies have indicated that psoriasis patients may have a higher risk of viral infections, pneumonia and sepsis, the latter only in erythrodermic psoriasis.[6, 7] Our results confirm that there is indeed an increased

risk of viral diseases accompanied by exanthema (e.g. smallpox, herpes simplex and zoster), viral CNS infections, both upper and lower respiratory tract infections and sepsis. Not only was the frequency of sepsis higher among subjects with severe psoriasis (crude HR=4.7, 95% CI 2.3-9.4), but also among mild psoriasis patients (incidence rate 44, 26 and 9 in severe psoriasis, mild psoriasis and reference subjects, respectively). A number of retrospective case series reported a higher infection rate in patients with psoriasis after arthroplasty, although others did not find a higher number of infected orthopedic prostheses.[25-28] The outcomes of our study suggest that psoriasis patients may indeed have more postoperative infections or infections of prosthetic devices.

Several factors may explain the higher likelihood of serious infections among subjects with more severe psoriasis. Although these subjects' susceptibility to IDs may be increased by systemic anti-psoriatic drugs, patients with more severe psoriasis may also have a higher prevalence of comorbidities, unhealthy life-style factors, and/or a higher low-grade inflammatory state which can affect their ID susceptibility.[29, 30] Rather than specifying therapy dose and duration prior to IDs for all subjects in this database, we instead used prescription fillings within a clinically relevant time window. We did not confirm that in the cohort of severe psoriasis patients, recent filling of systemic anti-psoriatic drug prescriptions were a significant predictor and explanation for this higher risk of IDs. In case of tuberculosis, some additional cases were expected to be detected among psoriasis patients because of screening guidelines prior to anti-TNF-alpha therapy initiation. However, there was no significantly different risk of tuberculosis between psoriasis and reference subjects.

We acknowledge the limitations of this study which includes the absence of data on lifestyle factors such as smoking, alcohol consumption, physical activity, obesity and socio-economical status. Neither did we adjust for chemotherapy use since this is usually given within an inpatient setting and is therefore not registered in outpatient drug dispensing records. The study outcomes are therefore likely to be affected by residual confounding.[1, 31, 32] A confounding effect of comorbidities was demonstrated by the significant effect of adjusting for drugs for diabetes or obstructive lung diseases, which appeared to be the strongest in patients with more severe psoriasis.

Misclassification, for example by including false-positive psoriasis cases, may have led to regression to the nil to demonstrate exposure-related disease since we based the definition of psoriasis on drug and hospitalization records. However, the proxies of disease were objectively measured avoiding other kinds of biases and prior validation showed a high sensitivity and good specificity. The prevalence of psoriasis is estimated to be 2-3% in Western populations.[33, 34] Our database showed a prevalence of 1.0% actively treated psoriasis patients (n=25,742). As expected, this was lower than the estimated population prevalence that also includes patients without prescription drugs. Another proportion was excluded due to the absence of prescriptions that we defined as being specific for psoriasis like as PUVA, fumaric acid, efalizumab,

topical vitamin-D derivatives or ditranol, the absence of a psoriasis inpatient treatment or other the presence of other exclusion criteria. The 12% prevalence of more severe psoriasis in the psoriasis cohort is reasonably consistent with a recent estimate of 17% moderate to severe psoriasis in US adults, which suggests a reliable reflection of psoriasis severity in the study population.[35] The use of process based measures to classify psoriasis severity nevertheless remains controversial since various factors besides the psoriasis severity affect the process of care. However, this therapy based classification is a reasonable and frequently used measure in the absence of data on the amount of affected skin.

A strength of this large population-based cohort study is that clinically relevant outcomes of hospital discharge diagnoses for IDs were used as endpoints. PHARMO collected data prospectively and irrespective of our hypothesis avoiding recall bias and the possibility of differential misclassification. The longitudinal National Medical Register from which the hospital data were extracted has almost complete coverage (99%) of all hospital admissions in the Netherlands. The impact of diagnostic bias is likely to be limited because only serious IDs were included in the analyses.

The findings of this observational study suggest that psoriasis patients have a tone and a half time higher risk of serious IDs which cannot be explained by exposure to systemic anti-psoriatic drugs and comorbidities associated with psoriasis.

References

1. Nijsten T , Wakkee M. Complexity of the association between psoriasis and comorbidities. J Invest Dermatol 2009;129:1601-3.
2. Hollox EJ, Huffmeier U, Zeeuwen PL, Palla R, Lascorz J, Rodijk-Olthuis D et al. Psoriasis is associated with increased beta-defensin genomic copy number. Nat Genet 2008;40:23-5.
3. Lande R, Gregorio J, Facchinetti V, Chatterjee B, Wang YH, Homey B et al. Plasmacytoid dendritic cells sense self-DNA coupled with antimicrobial peptide. Nature 2007;449:564-9.
4. Zeeuwen PL, de Jongh GJ, Rodijk-Olthuis D, Kamsteeg M, Verhoosel RM, van Rossum MM et al. Genetically programmed differences in epidermal host defense between psoriasis and atopic dermatitis patients. PLoS One 2008;3:e2301.
5. Henseler T , Christophers E. Disease concomitance in psoriasis. J Am Acad Dermatol 1995;32:982-6.
6. Lindegard B. Diseases associated with psoriasis in a general population of 159,200 middle-aged, urban, native Swedes. Dermatologica 1986;172:298-304.
7. Green MS, Prystowsky JH, Cohen SR, Cohen JI , Lebwohl MG. Infectious complications of erythrodermic psoriasis. J Am Acad Dermatol 1996;34:911-4.
8. Herings RM, Urquhart J , Leufkens HG. Venous thromboembolism among new users of different oral contraceptives. Lancet 1999;354:127-8.
9. Erkens JA, Panneman MM, Klungel OH, van den Boom G, Prescott MF , Herings RM. Differences in antihypertensive drug persistence associated with drug class and gender: a PHARMO study. Pharmacoepidemiol Drug Saf 2005;14:795-803.
10. Lau HS, de Boer A, Beuning KS , Porsius A. Validation of pharmacy records in drug exposure assessment. J Clin Epidemiol 1997;50:619-25.
11. www.pharmo.nl. Accessed November 10, 2009.
12. Herings RM, Leufkens HG , Vandenbroucke JP. Acute myocardial infarction and prior antibiotic use. JAMA 2000;284:2998-9.
13. WHO. WHO International Classification of Diseases, 9th revision, clinical modification, and HIV infection codes addendum (rev. nr. 1). Geneva, Switzerland: WHO; 1987.
14. WHO. WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment. Oslo, Norway: WHO; 1999.
15. Wakkee M, Meijer W, Neumann HA, Herings RM , Nijsten T. Psoriasis may not be an independent predictor for the use of cardiovascular and anti-diabetic drugs: a 5-year prevalence study. Acta Derm Venereol 2009;89:476-83.
16. Spuls PI, Bossuyt PM, van Everdingen JJ, Witkamp L , Bos JD. The development of practice guidelines for the treatment of severe plaque form psoriasis. Arch Dermatol 1998;134:1591-6.
17. Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ , Troxel AB. Risk of myocardial infarction in patients with psoriasis. Jama 2006;296:1735-41.
18. Simonsen L, Conn LA, Pinner RW , Teutsch S. Trends in infectious disease hospitalizations in the United States, 1980-1994. Arch Intern Med 1998;158:1923-8.
19. Koomen ER, Joosse A, Herings RM, Casparie MK, Bergman W, Nijsten T et al. Is statin use associated with a reduced incidence, a reduced Breslow thickness or delayed metastasis of melanoma of the skin? Eur J Cancer 2007;43:2580-9.
20. Shah BR , Hux JE. Quantifying the risk of infectious diseases for people with diabetes. Diabetes Care 2003;26:510-3.
21. Benfield T, Lange P , Vestbo J. COPD stage and risk of hospitalization for infectious disease. Chest 2008;134:46-53.

22. Martin RJ. Infections and asthma. Clin Chest Med 2006;27:87-98, vi.
23. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC , Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007;370:1453-7.
24. Hosmer DW, Jr. , Lemeshow S. Applied survival analysis: regression modelling of time to event data. New York:Wiley Interscience 1999.
25. Beyer CA, Hanssen AD, Lewallen DG , Pittelkow MR. Primary total knee arthroplasty in patients with psoriasis. J Bone Joint Surg Br 1991;73:258-9.
26. Drancourt M, Argenson JN, Tissot Dupont H, Aubaniac JM , Raoult D. Psoriasis is a risk factor for hip-prosthesis infection. Eur J Epidemiol 1997;13:205-7.
27. Hicken GJ, Kitaoka HB , Valente RM. Foot and ankle surgery in patients with psoriasis. Clin Orthop Relat Res 1994:201-6.
28. Stern SH, Insall JN, Windsor RE, Inglis AE , Dines DM. Total knee arthroplasty in patients with psoriasis. Clin Orthop Relat Res 1989:108-10; discussion 11.
29. Wakkee M , Nijsten T. Comorbidities in dermatology. Dermatol Clin 2009;27:137-47, vi.
30. Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB , Gelfand JM. Prevalence of cardiovascular risk factors in patients with psoriasis. J Am Acad Dermatol 2006;55:829-35.
31. Herron MD, Hinckley M, Hoffman MS, Papenfuss J, Hansen CB, Callis KP et al. Impact of obesity and smoking on psoriasis presentation and management. Arch Dermatol 2005;141:1527-34.
32. Poikolainen K, Karvonen J , Pukkala E. Excess mortality related to alcohol and smoking among hospital-treated patients with psoriasis. Arch Dermatol 1999;135:1490-3.
33. Nijsten T, Rolstad T, Feldman SR , Stern RS. Members of the national psoriasis foundation: more extensive disease and better informed about treatment options. Arch Dermatol 2005;141:19-26.
34. Stern RS, Nijsten T, Feldman SR, Margolis DJ , Rolstad T. Psoriasis is common, carries a substantial burden even when not extensive, and is associated with widespread treatment dissatisfaction. J Investig Dermatol Symp Proc 2004;9:136-9.
35. Kurd SK , Gelfand JM. The prevalence of previously diagnosed and undiagnosed psoriasis in US adults: results from NHANES 2003-2004. J Am Acad Dermatol 2009;60:218-24.

Chapter 7

Complexity of the association between psoriasis and comorbidities

T. Nijsten
M. Wakkee

J Invest Dermatol. 2009;129:1601-3.

Editorial for:Psoriasis and Osteoporosis: a sex-specific association?

Abstract

Multiple observational studies have recently demonstrated associations between psoriasis and several comorbidities—especially metabolic syndrome and cardiovascular disease, and now osteoporosis. It has been hypothesized that elevated levels of tumor necrosis factor-α are a biological explanation for the observed associations. In this commentary, we discuss the complexity of associations between psoriasis and comorbidities, possible residual confounding, the limitations of observational studies in proving causality, absolute versus relative risk differences, and the clinical relevance and possible clinical impact of "upgrading" psoriasis to a systemic disease.

Introduction

Several observational studies have recently demonstrated that psoriasis is associated with diseases other than psoriatic arthritis, including cardiovascular disease and metabolic syndrome, cancer, chronic obstructive pulmonary disease, depression, and, in this issue, osteoporosis.[1-5] The trend in scientific literature and meeting presentations has been to "upgrade" psoriasis from a cutaneous to a systemic disease. But before we consider accepting this hypothesis, which may have a considerable impact on the management of patients, the limitations of observational study designs and the available evidence should be reviewed.

Complexity of association

The direct link between psoriasis and many of the possibly associated diseases is the presence of chronic inflammation and, in particular, elevated levels of the multifunctional cytokine tumor necrosis factor-α. However, several other factors may play important roles and confound this association (Figure 1). First, psoriasis has a major impact on patients' lives and is associated with depressive symptoms in a relatively large proportion of patients.[6] Impaired health-related quality of life (HRQOL) may lead to unhealthy lifestyle behaviors such as smoking, alcohol consumption, decreased physical activity, and obesity, which are independent risk factors for many other diseases. Conversely, obesity and smoking may increase the risk of developing psoriasis[7, 8], suggesting that these may be primary risk factors for several comorbidities and that psoriasis is no more than an innocent bystander. The presence of psoriatic arthritis may further limit patients' physical functioning. In addition, psoriasis therapies (e.g., cyclosporine and prolonged

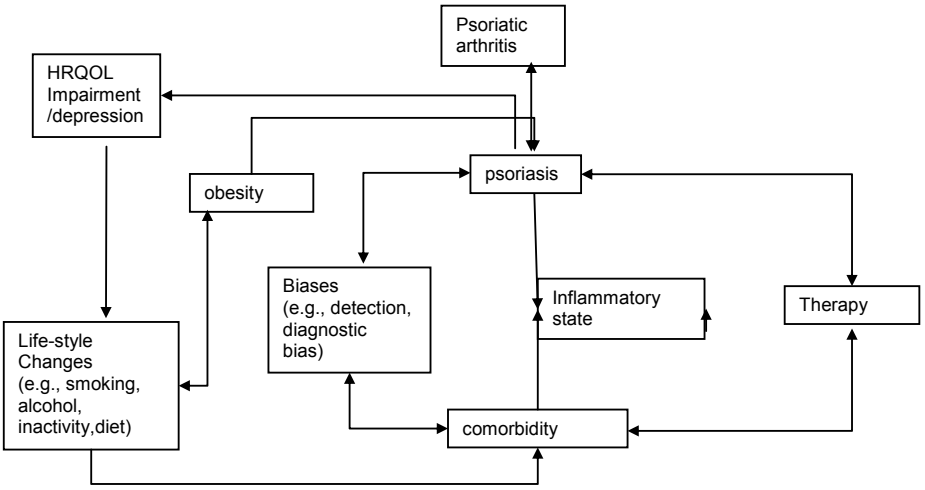

Figure 1. Schematic overview of possible factors influencing the association between psoriasis and comorbidities.

topical steroid use) may increase the risk of several comorbidities (e.g., cardiovascular risk and osteoporosis, respectively), and other drugs used to treat comorbidities may induce or exacerbate psoriasis (e.g., β-blockers and lithium). In addition to HRQOL impairment and (prior) drug exposure, several epidemiological biases may affect the association.

Most importantly, psoriasis patients are more likely to visit physicians because of their disease than "healthy" people from the general population, which puts them at risk for being screened for and diagnosed with other diseases. This detection bias is especially important in the diagnosis of common diseases that are typically underdiagnosed, such as hypertension and osteoporosis in men.[4] Moreover, most psoriasis patients have limited disease (affecting less than one palm-sized area[6]), and patients who seek medical care for their limited psoriasis are probably also more likely to seek care sooner for other conditions. Diagnostic bias may be important in evaluating the association between psoriasis and lymphomas[3, 9], because patients with cutaneous T-cell lymphoma (CTCL) may have initially been diagnosed with and registered as having psoriasis before their skin disease was diagnosed as CTCL, leading to a misclassification bias.

The detection of associations between psoriasis and comorbidities is challenging, because it has required the use of existing databases that were not designed for this purpose. Because the prevalence of most comorbidities is relatively low, large sample sizes are required to obtain sufficient power to test the associations. Therefore, health insurance data or existing large prospective (national) cohort studies have been required to include a sufficient number of patients (often more than 10,000 individuals). The limitation of these large datasets is that they usually have incomplete information -or none at all- about important confounders such as HRQOL, lifestyle factors, physical exercise, drug exposure, body mass index, and health-care consumption. Researchers may attempt to overcome these limitations by performing subgroup analyses or by creating proxies for missing confounders. For example, health-care consumption may be roughly estimated on the basis of number of drugs used or number of past diagnoses. The impact of including a proxy for health-care consumption is illustrated by the observation that, after adjusting for it, psoriasis patients were no longer significantly more likely to use cardiovascular drugs[10], and each additional diagnosis increased the risk of having osteoporosis by more than 20%.[4] Another example of the problem with using proxies in statistical models may be found in the osteoporosis study that assessed the role of decreased physical activity by hypothesizing that people with depression and/or blindness would be less likely to be physically active.[4] In fact, estimating physical activity is much more complex, and only a fraction of the actual level of physical activity may be ascertained in this way.

The observation by Dreiher et al.[4] that 56 of 100 diseases were associated with psoriasis raises the suspicion of residual confounding and the failure to address several biases. It is highly unlikely that psoriasis patients are at increased risk for developing the majority of these diseases

compared with patients without psoriasis. Although statistical multivariate models that adjust for available confounders were used, 90% of the variability of the association between psoriasis and osteoporosis was not captured by the included covariates, confirming the presence of residual confounding (estimated *R* square = 0.105).

Absolute versus relative risk versus clinical relevance

The use of very large study populations increases the likelihood of detecting statistically significant differences, because *P*-values depend on observed differences between cases and controls and on sample sizes. The absolute risk increment for developing comorbidities in psoriasis patients is almost always less than 5%. For example, the observed difference between patients and controls for developing osteoporosis was less than 2.5% (3.1% vs. 1.7% for men and 22.3% vs. 20.2% for women), but because the study included almost 8,000 patients, both differences were highly significant ($p < 0.0001$ and $p = 0.008$, respectively)[4]. The absolute risk almost doubles in men, but in women it increases by only about one-tenth. After adjusting for age, inflammatory bowel disease, and a number of chronic conditions in a multivariate logistic model, the increased risk for men with psoriasis having osteoporosis decreased from about twofold to about 35% compared with controls (adjusted odds ratio = 1.35; 95% confidence interval = 1.04–1.75), and the increased risk in women disappeared, despite the considerable residual confounding.[4]

The modest risk increments reported in this study should call into question their clinical relevance. Do the results of this study justify our classification of male psoriasis patients, without other risk factors, as being at high risk of developing osteoporosis, and should they receive bone mineral density scans? From this perspective, it would be interesting to know the number of patients required to diagnose one additional case of osteoporosis. The National Psoriasis Foundation advised physicians to adhere to the existing national guidelines for monitoring patients for cardiovascular disease and not to monitor all psoriasis patients independent of other risk factors. This recommendation is wise, because it reminds us that dermatologists are physicians who should look beyond the skin, it does not stigmatize psoriasis patients, and it acknowledges that causality has not yet been proved.

Association versus causality

The strength of observational studies is in generating hypotheses, but their limitation is their inability to generate results that allow researchers to differentiate clearly between association and causality. The likelihood of observing a causal relation increases when there is a clear biological explanation for the association, the association is confirmed in multiple studies, and there is a dose–response relationship and a clear temporal relationship between exposure

and outcome. The increased inflammatory status of psoriasis patients with high levels of the multifunctional cytokine tumor necrosis factor-alpha is often proposed as the biological explanation for the association between psoriasis and several comorbidities, including osteoporosis. Multiple epidemiological studies, but not all, have indicated that these patients are at increased risk for cardiovascular disease compared with the general population. Patients with moderate to severe psoriasis (i.e., patients who have used systemic drugs and/or have been hospitalized for psoriasis) seem to be at higher risk for cardiovascular disease than patients with mild disease, indicating that there is a "dose–response" relationship.[1, 2] Whether psoriasis precedes the comorbidities or vice versa is difficult to assess, but some risk factors for cardiovascular disease may induce or exacerbate psoriasis. For example, a prospective cohort study suggested that obese US nurses were at higher risk for developing psoriasis, and an Italian case–control study indicated that smoking may induce psoriasis.[7, 8] For other comorbidities, such as chronic obstructive pulmonary disease and osteoporosis, additional studies are warranted to confirm the recent findings and to assess dose–response and temporal relationships before causality can be assumed. Ultimately, a need exists for large prospective cohorts that include incident psoriasis patients to confirm causality between psoriasis and other diseases.

Possible clinical impact

In contrast to other chronic inflammatory diseases such as rheumatoid arthritis, inflammatory bowel disease, and multiple sclerosis, cutaneous psoriasis does not progress to irreversible organ damage. Psoriasis often affects less than 3% of the body surface area, waxes and wanes, and can often be treated topically, making it a relatively mild disease from a public health, scientific, and financial perspective. Because this view contrasts with patients' perceptions, the dermatological community has embraced the "outcome movement"; by including patient-reported outcomes such as HRQOL in the definition of disease severity, the proportion of psoriasis patients reported to have moderate to severe disease has increased considerably. The measurement of the impact of psoriasis on patients' lives may affect the allocation of limited resources and the management of psoriasis (via an increase in patient participation, the use of psychological counseling, continuous control of the disease, and, consequently, the use of systemic therapies). "Upgrading" psoriasis to a systemic disease may affect patient care in the long term by increasing adherence to existing screening guidelines for common internal diseases. However, it is also likely that in the near future, in line with current rheumatoid arthritis treatment, it will be suggested that more aggressive treatment of psoriasis may limit the clinical extent of the disease and/or decrease patients' long-term risk of developing comorbidities such as cardiovascular disease. As noted above, before we accept this interesting and possibly important premise, more stringent clinical evidence should be weighed against other factors, such as clinical relevance and the risk–benefit ratios of therapies and costs.

Conclusion

The ultimate question is whether statistically significant findings in observational studies indicate not only causality but also clinical relevance. Taking into consideration the designs of studies, some inconsistencies in the findings, residual confounding, and the relatively modest risk estimates, caution is warranted before psoriasis patients are screened and treated differently than other patients independent of other risk factors. Most importantly, the recent comorbidity studies reinforce the need to treat the whole patient, reminding dermatologists that they are physicians first—physicians with a special interest in skin.

References

1. Mallbris L, Akre O, Granath F, et al. Increased risk for cardiovascular mortality in psoriasis inpatients but not in outpatients. Eur J Epidemiol 2004;19(3):225-30.
2. Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB. Risk of myocardial infarction in patients with psoriasis. Jama 2006;296(14):1735-41.
3. Gelfand JM, Shin DB, Neimann AL, Wang X, Margolis DJ, Troxel AB. The risk of lymphoma in patients with psoriasis. J Invest Dermatol 2006;126(10):2194-201.
4. Dreiher J, Weitzman D, Cohen AD. Psoriasis and osteoporosis: a sex-specific association? J Invest Dermatol 2009;129(7):1643-9.
5. Dreiher J, Weitzman D, Shapiro J, Davidovici B, Cohen AD. Psoriasis and chronic obstructive pulmonary disease: a case-control study. Br J Dermatol 2008.
6. Stern RS, Nijsten T, Feldman SR, Margolis DJ, Rolstad T. Psoriasis is common, carries a substantial burden even when not extensive, and is associated with widespread treatment dissatisfaction. J Investig Dermatol Symp Proc 2004;9(2):136-9.
7. Naldi L, Chatenoud L, Linder D, et al. Cigarette smoking, body mass index, and stressful life events as risk factors for psoriasis: results from an Italian case-control study. J Invest Dermatol 2005;125(1):61-7.
8. Setty AR, Curhan G, Choi HK. Obesity, waist circumference, weight change, and the risk of psoriasis in women: Nurses' Health Study II. Arch Intern Med 2007;167(15):1670-5.
9. Stern RS. Lymphoma risk in psoriasis: results of the PUVA follow-up study. Arch Dermatol 2006;142(9):1132-5.
10. Wakkee M, van der Linden M, Nijsten T. Psoriasis appears not to be directly related with using cardiovascular and antidiabetic drugs. J Invest Dermatol 2008;128:2548.

Chapter 8

Knowledge, attitudes and use of the guidelines for the treatment of moderate to severe plaque psoriasis among Dutch dermatologists

M. Wakkee
M. Lugtenberg
P.I. Spuls
E.M. de Jong
H.B. Thio
G.P. Westert
T. Nijsten

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Abstract

Background In 2003, the Dutch psoriasis guidelines were among the first evidence-based medicine guidelines in dermatology. Although pivotal, the implementation of dermatological guidelines has not been assessed.

Objectives To evaluate various aspects that affect implementation of clinical guidelines such as knowledge, attitudes and practices among dermatologists.

Methods A cross-sectional anonymous postal survey was conducted among all Dutch dermatologists. In addition to questions about knowledge and practices, 24 items assessed guidelines attitudes. Factor analysis was applied to merge these items into attitudinal scales and multiple linear regression was used to identify predictors for these scales.

Results Of the 353 dermatologists, 161 (46%) completed the questionnaire. Almost all respondents were aware of the guidelines and 60% reported to have a decent knowledge of their content. Factor analysis retained 22 items divided into three scales: usefulness and content, barriers, and reliability. Apart from some disagreement on the user-friendliness and communication facilitating properties, the dermatologists' attitudes were generally positive. A larger volume of patients with psoriasis was associated with more frequent use of the guidelines [adjusted odds ratio (OR) = 2.42; 95% confidence interval (CI) 1.02–5.72]. Good familiarity predicted a more positive attitude towards the guidelines' usefulness and content ($P < 0.001$), perceived barriers ($P < 0.001$), and more frequent use in practice (adjusted OR = 8.38; 95% CI 3.08–22.81).

Conclusions Dutch dermatologists seem to know and appreciate their psoriasis guidelines and use them more often when they have a larger psoriasis population. Enhancing the familiarity of the guidelines among users may result in a more positive attitude towards them and a higher frequency of use.

Introduction

In 2003, the Dutch Society for Dermatology and Venereology (NVDV) together with the Dutch Institute for Healthcare Improvement introduced national practice guidelines for the treatment of moderate to severe chronic plaque-type psoriasis in the Netherlands.[1] These psoriasis guidelines were among the first national guidelines in dermatology. For each treatment, efficacy, safety, patients' perspectives, costs and follow-up were evaluated.[2] An updated version was presented in 2005 including an additional chapter on biological treatments.[3] The Dutch psoriasis guidelines were used as the basis for the recently published German guidelines on the treatment of psoriasis vulgaris.[4]

Experts on psoriasis developed the guidelines by a commonly accepted methodology of evidence-based guideline development, based on evidence from scientific literature and consensus among experts when the literature is insufficient.[5] The Appraisal of Guidelines Research and Evaluation (AGREE) instrument, which is considered a standard instrument in the quality assessment of guidelines, emphasizes the need for an evaluation after the introduction of a guideline (item: 'the evaluation of implementation of the developed guideline over time').[6] The implementation of dermatological guidelines has rarely been reported; one Australian survey evaluated the management of primary cutaneous melanomas before and after the publication of the melanoma guidelines and a small survey among 42 Scottish dermatologists assessed their management of basal call carcinoma and compared this with the existing guidelines.[7, 8] Some surveys were conducted as a prelude to consensus conferences, of which one was actually followed by a survey to examine the impact of the guidelines.[9-11] Past evaluations of the Dutch psoriasis guidelines focused on specific sections such as adherence to the guidelines with respect to methotrexate treatment or home ultraviolet B phototherapy, but none evaluated the implementation of the complete psoriasis guidelines.[12, 13] Although there are many dermatological guidelines, very few have been evaluated and none has used a standardized instrument. The psoriasis guidelines have been introduced in multiple ways, trying to reach all Dutch dermatologists, including approval by the member meeting of the NVDV, postal delivery of hard copy with a summary card, online access, publication in Dutch medical journals, and presentations and discussion forums at national meetings. However, it has been demonstrated that changing physicians' behaviour is extremely difficult.[14] From a psychological perspective, this is called the 'knowledge–behaviour gap', implicating the difference between what we know we should do and what we actually do in clinical practice.[14, 15]

The objective of this survey is to assess the implementation of the Dutch psoriasis guidelines by focusing on awareness, knowledge, attitudes and use of the guidelines among a large sample of Dutch dermatologists. In addition, an instrument for the evaluation of guidelines is presented and multivariate models were used to investigate physicians' and practice characteristics that were associated with the study outcomes.

Materials and methods

Study design and population

An anonymous postal survey was conducted among the 357 members of the NVDV. Between January and May 2007, all members received a letter announcing our survey, two full questionnaires and two reminder letters. Dermatologists were given the opportunity to excuse themselves from further mailings after the first round by calling, writing, or e-mailing to one of the investigators. At several regional and national meetings dermatologists were motivated to return the questionnaire.

Questionnaire content

The 12-page, standardized questionnaire consisted of 44 questions and was divided into five sections. The first part assessed demographic as well as professional characteristics of the dermatologists such as age, sex, residency programme, years in practice, time spent weekly on patient contacts, and type of practice. The second section assessed the familiarity and attitudes towards and use of the current Dutch guidelines on moderate to severe plaque psoriasis. Views on the guidelines were examined with 24 statements, based on 14 items from the 'Attitudes Towards Guidelines' scale, which we extended with 10 additional statements related to guideline attitudes.[16] In addition, 11 questions were asked to assess the motivation of using guidelines. The last section questioned dermatologists on their experience with traditional and biological therapies of psoriasis and the reimbursement criteria of the biologicals.[17]

The survey included multiple response formats. Demographic and practice items were categorical variables. Age was categorized into 10-year subgroups to respect responders' privacy. Attitudinal questions (1, strongly disagree; 5, strongly agree), familiarity with the guideline (1, none; 5, very good), and frequency of use (1, never; 5, always) were scored on a five-point Likert scale with free space at the end of the question for additional suggestions.

Statistical analysis

The proportion of responders was calculated as a percentage from the eligible population. We used the χ^2 test to determine the statistical significance of differences in the distribution of the categorical variables age and gender between responders and nonresponders.

To reduce the number of dependent variables and improve the interpretation of the data, an exploratory factor analysis was performed to examine the underlying dimensions of the 24 items that assessed guideline attitudes. Factor analysis is based on the assumption that items (e.g. questions) sharing similar underlying dimensions are highly correlated and items that measure

dissimilar dimensions yield low correlations. On the basis of this assumption, factor analysis is able to assign items to scales and each scale reflects a different dimension.[18] For this analysis, principal axis factor (PAF) analysis was used followed by oblique rotation, which assists in achieving a simpler and theoretically more meaningful factor pattern by assuming that the factors will be correlated.[18] For determining the number of factors to be retained, the Kaiser–Guttman rule (i.e. eigenvalue > 1) was applied first, followed by Cattell's scree test. An eigenvalue > 1 indicates that more common variance than unique variance is explained by that factor.[18] The scree test focuses on the magnitude of changes in eigenvalues from factor to factor and identifies the most appropriate factor solution when the eigenvalues decrease minimally at subsequent factors. Items with loadings of 0.40 or higher were assigned to a factor. If item loadings were less than 0.40 and/or showed a difference of less than 0.10 on multiple factors, they were eliminated from the analysis (i.e. item complexity).[19]

Multivariate linear regression analyses investigated the association between dermatologists' characteristics including their familiarity with the guidelines and the retained factors of the attitudes towards the psoriasis guidelines. Independent variables included were gender, duration of certification (continuous variable), type of practice (none, peripheral, academic, both), days of patient care a week (3 days or less, 4 days or more), number of patients with psoriasis per month (less than 15 or more than 15), familiarity with the guidelines (not to moderate or good to very good). As age was only determined per category, duration of certification, which is a proxy for age, was included in the multivariate model. The presence of multicollinearity was tested by determining the variance inflation factor (VIF) and tolerance value per variable. Cut-off values were a VIF > 4 and tolerance < 0.25.[20] The above-mentioned independent variables were also used in multivariate logistic regression models to examine determinants of the familiarity with the guidelines (none to moderate or good to very good) and the frequency of using the guidelines (never to sometimes or usually to always).

Results

Study population

Of the 357 members of the NVDV, four dermatologists were excluded because they were retired or no longer active as a dermatologist. Among the remaining 353 dermatologists, the overall response rate was 46% (161/353) and three responders returned the questionnaire without answering a single item. The characteristics of the 161 respondents are presented in Table 1. About 60% were men and 65% were aged 45 years or older. Almost 80% were affiliated to nonacademic hospitals, with about two-thirds working at least 4 days a week and 53% seeing more than 15 patients with psoriasis monthly. Nonresponders did not differ significantly from responders with respect to age and gender (P = 0.16 and P = 0.64, respectively). The working affiliation of the

respondents also showed a comparable distribution as described in the original population in 2004, with 72% working in a nonacademic hospital and 23% in an academic hospital.[13]

Table 1. Demographic and professional characteristics of dermatologists (n = 161)

Demographics and characteristics	n*	%*
Gender		
Male	101	62.7
Female	60	37.3
Age		
25-34 years	9	5.6
35-44 years	48	29.8
45-54 years	60	37.3
55-64 years	38	23.6
> 65 years	6	3.7
Year of registration as a dermatologist		
Before 1980	15	9.3
Between 1980-1989	45	28.0
Between 1990-1999	54	33.5
After 2000	40	24.8
Practice type		
Peripheral hospital	128	79.5
University hospital	33	20.5
Days committed to patient care		
2 days a week or less	15	9.3
3 days a week	40	24.8
4 days a week	65	40.4
5 days a week	39	24.2
Number of psoriasis patients seen monthly		
< 5 patients	15	9.3
5 – 15 patients	51	31.7
> 15 patients	86	53.4

* Number may not add up to 161 and percentages may not add up to hundred percent due to missing values.

Factor analysis

Factor analysis resulted in six factors with an eigenvalue > 1.0. However, a scree plot suggested a three-factor or four-factor solution. Therefore, both solutions were investigated with PAF analysis using oblique rotation to evaluate for simple structure. The three-factor solution seemed most meaningful in describing the dimensionality of attitudes towards the guidelines (Table 2). Factor 1 comprised 11 items that addressed how responders rated the usefulness and content of the guidelines, factor 2 contained nine items which were related to practical and organizational barriers, and the two items of factor 3 assessed the perceived reliability of the guidelines. Two items showed item complexity, 'show too little consideration for the wishes of the patient' and 'challenge the autonomy of care providers'. Because of their important and unique content, they were classified into the factor they most logically represented, factor 1 and 2, respectively. Of the 24 items, the retained 22 accounted for 44% of the total variance and the Cronbach's alpha of the factors were 0.79, 0.83 and 0.79.

Table 2 Principal axis factor analysis with oblique rotation of the items assessing the attitudes towards the guidelines[a]

Item	Factor 1[b]	Factor 2[b]	Factor 3[b]
In practice well feasible[c]	0·793		
Clear and specific[c]	0·740		
Useful as educational tool[c]	0·718		
User-friendly[c]	0·707		
Resemble daily practice[c]	0·697		−0·220
A convenient source of advice[c]	0·605		
Meet my expectations[c]	0·561		
Represent the latest state of science[c]	0·502		
Can facilitate communication with patients[c]	0·427		
Can improve the quality of health care[c]	0·426		
Show too little consideration for the wishes of the patient[c]	−0·392	0·251	0·412
Implementation is too expensive for us[d]		0·748	
I have not seen these guidelines in our health care unit[d]		0·628	−0·285
Difficult to find if needed[d]		0·596	
Not valued in our organization[d]	−0·262	0·594	
Oversimplify medical practice[d]		0·536	0·210
Occupational competence is insufficient for adopting the latest guidelines[d]		0·527	
Most of our team members have disapproving attitudes about these guidelines[d]		0·486	
Implementation is not possible because of pressure of work and lack of time[d]	−0·264	0·474	0·251
Challenge the autonomy of care providers[d]		0·413	0·367
Based on scientific evidence[e]	0·300	−0·286	0·560
Made by experts[e]	0·271	−0·213	0·540
Represent the opinion of a limited group of colleagues	−0·388	0·220	
Need to be updated more than once every 5 years			0·203
Cronbach's alpha	0·794	0·831	0·788

[a]Principal axis factor analysis reduces the data into theoretically meaningful underlying dimensions and oblique rotation helps to achieve a simpler, theoretically more meaningful factor pattern by assuming that the factors will be correlated. [b]Loading of the items on the different factors. Absolute values of < 0·20 are suppressed. As a general rule, variables with large loadings indicate that they are representative of the factor, while small loadings suggest that they are not. [c]Factor 1: usefulness and content. [d]Factor 2: practical and organizational barriers. [e]Factor 3: reliability.

Knowledge, attitudes and use of guidelines

Nearly all (96%) participating dermatologists were aware of the existence of the national psoriasis guidelines and almost 70% also knew about the chapter on biological therapies that was added in 2005. Overall, 60% self-rated their knowledge of the guidelines as good to excellent.

Attitudes towards the usefulness and content of the guidelines varied from more than 70% of the participants who thought they can improve the quality of health care to 31% who agreed they can facilitate communication with patients and families (Figure 1). However, 17% of the responders agreed that the current guidelines showed too little consideration for the wishes of the patient. Their usefulness as an educational tool as well as a convenient source of advice found agreement in 60% of the responders, although only 33% considered the guidelines user-friendly. Assessment

of practical and organizational barriers for implementation showed that the availability of the guidelines was extremely high. More than 60% disagreed with the statement that guidelines are not valued in their organization or are too expensive to implement and half of the responders disagreed that these guidelines oversimplify medical practice or challenge their autonomy. They were considered reliable guidelines: approximately 80% thought these guidelines were based on scientific evidence and made by experts. Less than a quarter of the participants indicated that the guidelines represent the opinion of a small group of experts. About 60% indicated that an update of these guidelines should occur more than once every 5 years.

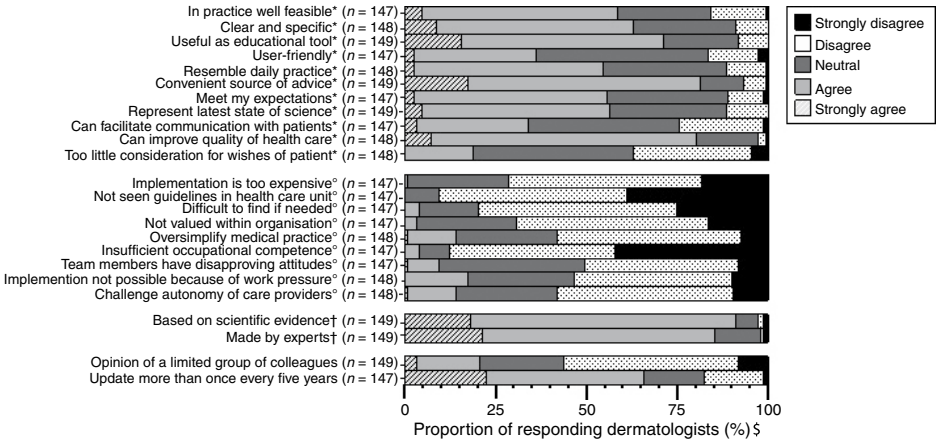

Figure 1. Attitudes towards psoriasis guidelines.
*Factor 1: usefulness and content; °Factor 2: practical and organizational barriers; †Factor 3: reliability.
$Distribution of responses among participants who completed the corresponding item.

Three-quarters of the participating dermatologists used the guidelines in daily practice. Most physicians used the hard copy and about a third used them sometimes and another third on a more regular basis. Reasons for implementing the guidelines are presented in Figure 2. Checking for contraindications (85%) and efficacy of therapy (76%) were the most common reasons for using these guidelines, while they were least frequently used for medical–legal grounds or as a part of visitation (44% and 40%, respectively).

Determinants of knowledge of guidelines

Multivariate logistic regression did not show any significant associations between the variables presented in Table 1, such as gender, duration of certification, type of practice, days of patient care a week, and number of patients with psoriasis seen monthly, and the degree of awareness of the guidelines (data not shown).

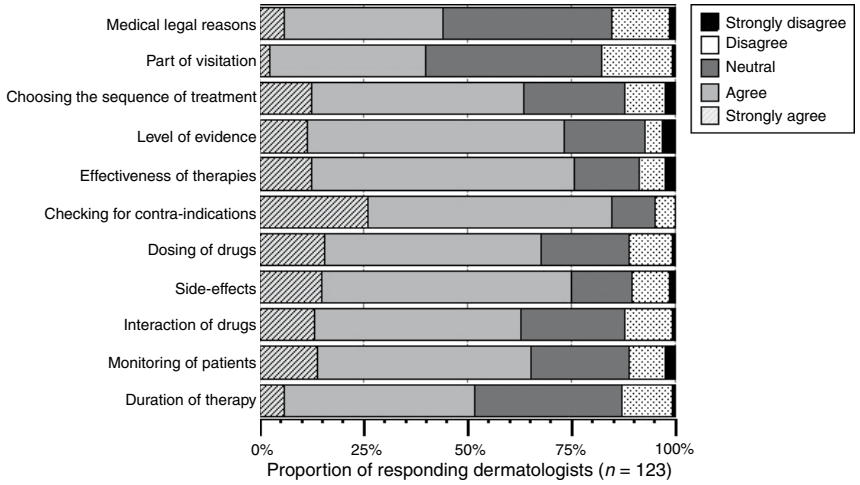

Figure 2. Reasons for implementing the guidelines.

Determinants of attitudes towards guidelines

Collinearity statistics did not show any variables with a VIF > 4 or a tolerance < 0.25. Therefore, all previously described physician and practice setting characteristics as well as the familiarity with the guidelines were included in the multivariate linear regression.

None of the dermatologists' characteristics was a significant predictor for any of the attitude scales. Good to very good familiarity with the guidelines was the only variable that was significantly associated with a more positive attitude towards the usefulness and content (B = 0.32, P < 0.001) as well as the practical and organizational barriers scale (B = 0.39, P < 0.001) after adjusting for gender, duration of certification, type of practice, days of patient care a week and number of patients with psoriasis seen monthly.

Determinants of self-reported use of guidelines

Multivariate logistic regression of personal and professional characteristics showed that responding dermatologists who saw more than 15 patients with psoriasis monthly were two times more likely to use the guidelines than those who saw fewer than 15 patients with psoriasis monthly [adjusted odds ratio (OR) = 2.42; 95% confidence interval (CI) 1.02–5.72]. Adding the degree of familiarity with the guidelines showed that those responders with good to very good familiarity were eight times more likely to use them more frequently (adjusted OR = 8.38; 95% CI 3.08–22.81). After adding the different attitude scales to the multivariate logistic regression, a more positive attitude towards the usefulness and content scale (adjusted OR = 3.57; 95% CI 1.45–8.81) as well as the practical and organizational barriers scale (adjusted OR = 2.58; 95% CI 1.10–6.04) was significantly associated with more frequent use of the guidelines.

Discussion

This survey revealed that among the responding Dutch dermatologists there is a high self-reported awareness and familiarity with the Dutch psoriasis guidelines. A review of 46 surveys on the awareness of guidelines and 31 surveys on the familiarity with guideline recommendations found a median unawareness rate of 54% and a unfamiliarity rate of 57%.[14] However, in our study almost all responders were aware of the existence of the guidelines, which may be due to the effort of distributing the guidelines among the members of the NVDV, selection bias (i.e. those responding are more likely to be aware than the nonresponders) or ascertainment bias (i.e. physician self-report of awareness may affect our findings but it is likely to be limited).[21] These same remarks also apply to the high reported familiarity, although the degree of familiarity showed some variation, with 35% reporting only a limited to moderate familiarity. In multivariate models, no physician characteristics were predictive for the level of familiarity with the guidelines.

Three scales were formatted out of the 24 items that assessed the attitudes towards these guidelines. The two questions that showed mild item complexity were considered to provide unique information and were, therefore, included in the most appropriate scales. Inspection of the factor loadings, content validity and the high internal consistency suggests that the factor analyses resulted in three meaningful scales. Nevertheless, it remains an exploratory factor analysis that needs to be confirmed in future validation studies.

The views towards the usefulness and content of the guidelines were overall supportive, with a majority of dermatologists judging them as an instrument that can improve the quality of health care, and serve as an educational tool and convenient source of advice. However, many dermatologists question whether the psoriasis guidelines facilitate patient communication and their user-friendliness, which is not surprising because the guidelines consist of 120 pages (and a summary card). Easy-to-use, concise evidence summaries may improve the user-friendliness of the guidelines. The costs of implementation, the guidelines' availability and appreciation in organizations were not considered as practical or organizational barriers for implementation and half of the responders disagreed that guidelines were oversimplifying or challenged their autonomy. In contrast to our findings, other Dutch medical specialists and pharmacologists perceived organizational and financial barriers to be of importance.[22, 23] Assessment of the perceived reliability showed that, in accordance with other studies, dermatologists indicated confidence in guidelines that were developed by their own society.[24, 25] The associations between greater familiarity with the psoriasis guidelines and better attitudes towards their usefulness and content as well as the practical and organizational barriers were to be expected, and confirm the internal validation of this survey. Further enhancing familiarity with the guidelines may overcome possible barriers that prevent dermatologists from using them.

Although the frequency varied, most respondents used the psoriasis guidelines but a quarter did not use them at all in daily practice. The self-assessment of physician practice may over- or underestimate actual practice when compared with chart audits or patient surveys.[26-28] To limit this ascertainment bias, the survey was strictly anonymous. The most important motivations for implementing the guidelines were therapy related, such as checking for contraindications, efficacy and adverse events.

Dermatologists who cared for a larger volume of patients with psoriasis more frequently used the guidelines, confirming their usefulness in daily practice. Positive attitudes towards usefulness and content as well as the practical and organizational barriers were associated with increased use of the guidelines. Responders who were more familiar with the guidelines had a more positive attitude towards them and used them more often, suggesting that the 'knowledge–behaviour gap' is limited in this population.

This is one of the first extensive evaluations of a (national) guideline in dermatology among more than 150 dermatologists. Based on an existing questionnaire and additional items, an instrument and its scales were created using factor analysis. Despite multiple attempts to motivate peers to complete the questionnaire, the response rate was only 46% (161 responders). However, the specific content and extensiveness of the survey make it likely that at least one dermatologist of most of the approximately 130 dermatological partnerships in the Netherlands, with particular interest in the treatment of psoriasis, participated. It has also been demonstrated that physicians adapt to their colleagues of the particular hospital in which they work and that the social environment in which physicians work is more important for their medical behaviour than their formal professional education.[29] Taking this perspective into account, the results of this survey are probably a good representation of the dermatological care for psoriasis in the Netherlands, perhaps even better than initially would be expected from the individual level response rate. A study on the effects of nonresponse bias in mail surveys of physicians showed that higher response rates across different medical specialties were not always associated with lower response bias. Although increasing response rates can reduce or eliminate response bias for some variables, it is more important to assess correctly their potential consequences on survey estimates.[3] The strictly anonymous study design assured that responders could freely express their opinion, but limited the comparison of responders and nonresponders. No difference was found for age categories and gender, but it is likely that responders were more familiar, had positive attitudes and used the guidelines more frequently compared with nonresponders. Even though the findings of this study cannot be generalized to all Dutch dermatologists, they do reflect the views and opinions of those who actually use the guidelines and examined factors associated with the outcomes. Unfortunately, because of the likely response bias it was not possible to explore the characteristics of dermatologists who do not use the guideline and their underlying motivations. Although difficult, in future

research it would be interesting to examine the rationale of dermatologists who do not use the guidelines to improve the implementation rates further.

In conclusion, 5 years after the introduction of the Dutch psoriasis guidelines, they seem to be well known, appreciated and considered reliable. The degree of familiarity with the guidelines was the single most important predictor of a more positive attitude of dermatologists towards the guidelines and frequency of using them. Hopefully, other countries with national dermatology guidelines will also assess the implementation of their guidelines and the attitudes towards the guidelines among their end-users.

Acknowledgments

We thank all participating dermatologists. This study was funded by an unrestricted grant from Merck-Serono, Schering-Plough and Wyeth.

References

1. CBO. Richtlijn Foto(Chemo)Therapie en Systemische Therapie bij Ernstige Chronische Plaque Psoriasis. Alphen a/d Rijn, The Netherlands: van Zuiden Communications, 2003.
2. Spuls PI, Tuut MK, van Everdingen JJ, de Rie MA. The practice guideline 'Photo(chemo)therapy and systemic therapy in severe chronic plaque-psoriasis. Ned Tijdschr Geneeskd 2004;148(43):2121-5.
3. CBO. Richtlijn Foto(Chemo)Therapie en Systemische Therapie bij Ernstige Chronische Plaque Psoriasis. 2005. Available at: http://www.cbo.nl/product/richtlijnen/folder20021023121843/rl_psoriasis_2005.pdf/view (last accessed 3 May 2008).
4. Nast A, Kopp IB, Augustin M, et al. Evidence-based (S3) guidelines for the treatment of psoriasis vulgaris. J Dtsch Dermatol Ges 2007;5 Suppl 3:1-119.
5. van Everdingen JJE, Burgers JS, Assendelft WJJ et al. Evidence-Based Richtlijnontwikkeling. Een Leidraad Voor de Praktijk. Houten, The Netherlands: Bohn Stafleu van Loghem, 2004; 353–62.
6. The AGREE Collaboration. Appraisal of Guidelines for Research & Evaluation (AGREE) Instrument. In: www.agreecollaboration.org. Accessed 1 february 2008.
7. Kelly JW, Henderson MA, Thursfield VJ, Slavin J, Ainslie J, Giles GG. The management of primary cutaneous melanoma in Victoria in 1996 and 2000. Med J Aust 2007;187(9):511-4.
8. Gudi V, Ormerod AD, Dawn G, et al. Management of basal cell carcinoma by surveyed dermatologists in Scotland. Clin Exp Dermatol 2006;31(5):648-52.
9. Bernard P, Christmann D, Morel M. Management of erysipelas in French hospitals: a post-consensus conference study. Ann Dermatol Venereol 2005;132(3):213-7.
10. Fontaine J, Beauchet A, Saiag P. National survey of dermatologists. Ann Dermatol Venereol 2002;129(4 Pt 2):551-8.
11. Barbarot S, Beauchet A, Zaid S, Lacour JP. The management of atopic dermatitis in children by dermatologists, paediatricians, general practitioners and allergologists: a national survey on practice patterns. Ann Dermatol Venereol 2005;132 Spec No 1:1S283-95.
12. Berends MA, de Jong EM, van de Kerkhof PC, Gerritsen MJ. Dermatologists' adherence to the guideline of the Dutch Society of Dermatology and Venereology with respect to the treatment with methotrexate for severe chronic plaque psoriasis: results from a Dutch survey. Dermatology 2007;215(1):45-52.
13. Koek MB, Buskens E, Bruijnzeel-Koomen CA, Sigurdsson V. Home ultraviolet B phototherapy for psoriasis: discrepancy between literature, guidelines, general opinions and actual use. Results of a literature review, a web search, and a questionnaire among dermatologists. Br J Dermatol 2006;154(4):701-11.
14. Cabana MD, Rand CS, Powe NR, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. Jama 1999;282(15):1458-65.
15. Grol R, Grimshaw J. From best evidence to best practice: effective implementation of change in patients' care. Lancet 2003;362(9391):1225-30.
16. Elovainio M EM, Mäkelä M. Attitudes towards guidelines and a scale for measuring them. In: Changing Professional Practice. Theory and Practice of Clinical Guidelines Implementation (Thorsen T, Mäkelä M, eds). Copenhagen: Danish Institute for Health Services Research and Development, 1999; 153–67.
17. Wakkee M, Thio HB, Spuls PI, de Jong EM, Nijsten T. Evaluation of the reimbursement criteria for biological therapies for psoriasis in the Netherlands. Br J Dermatol 2008.
18. Gorusch RL. Factor Analysis. Philadelphia, PA: W.B. Saunders, 1974.
19. Ho R. Handbook of Univariate and Multivariate Data Analysis and Interpretation with SPSS. Boca Raton, FL: Chapman and Hall–CRC, 2006; 203–38.
20. Fox J. Regression Diagnostics. Quantitative Applications in the Social Sciences. Thousand Oaks, CA: Sage Publications, 1991.

21. Cabana MD, Rand CS, Becher OJ, Rubin HR. Reasons for pediatrician `nonadherence to asthma guidelines. Arch Pediatr Adolesc Med 2001;155(9):1057-62.
22. Dijkstra RF, Braspenning JC, Uiters E, van Ballegooie E, Grol RT. Perceived barriers to the implementation of diabetes guidelines in hospitals in The Netherlands. Neth J Med 2000;56(3):80-5.
23. Fijn R, Brouwers JRBJ, de Jong-van den Berg LTW. Cross-sectional pharmacotherapeutic coherence in the Netherlands. Int J Pharm Pract 1999;7:159–66. 24. Tunis SR, Hayward RS, Wilson MC, et al. Internists' attitudes about clinical practice guidelines. Ann Intern Med 1994;120(11):956-63.
25. Hayward RS, Guyatt GH, Moore KA, McKibbon KA, Carter AO. Canadian physicians' attitudes about and preferences regarding clinical practice guidelines. CMAJ 1997;156(12):1715-23.
26. Weingarten S, Stone E, Hayward R, et al. The adoption of preventive care practice guidelines by primary care physicians: do actions match intentions? J Gen Intern Med 1995;10(3):138-44.
27. Leaf DA, Neighbor WE, Schaad D, Scott CS. A comparison of self-report and chart audit in studying resident physician assessment of cardiac risk factors. J Gen Intern Med 1995;10(4):194-8.
28. Montano DE, Phillips WR. Cancer screening by primary care physicians: a comparison of rates obtained from physician self-report, patient survey, and chart audit. Am J Public Health 1995;85(6):795-800.
29. de Jong JD, Westert GP, Lagoe R, Groenewegen PP. Variation in hospital length of stay: do physicians adapt their length of stay decisions to what is usual in the hospital where they work? Health Serv Res 2006;41(2):374-94.
30. McFarlane E, Olmsted MG, Murphy J, Hill CA. Nonresponse bias in a mail survey of physicians. Eval Health Prof 2007;30(2):170-85.

Chapter 9

Evaluation of the reimbursement criteria for biological therapies for psoriasis in the Netherlands.

M. Wakkee
H.B. Thio
P.I. Spuls
E.M. de Jong
T. Nijsten

Br J Dermatol. 2008 May;158(5):1159-61.

Sir, In Europe, biologicals are approved for moderate to severe plaque psoriasis in patients unresponsive, intolerant or with contraindications to conventional therapies such as psoralen plus ultraviolet (UV) A (PUVA), methotrexate and ciclosporin.[1] Subsequently, national reimbursement criteria were developed based on the approved indication (Table 1).[2] In some countries patients should have failed photo(chemo)therapy and methotrexate and ciclosporin, while in others failure of one or two systemic therapies is sufficient for reimbursement of biologicals. In the U.S.A. candidates for any systemic therapy are also eligible for a biological.

In the Netherlands, the evaluation of adherence to reimbursement criteria is carried out by a subcommittee of an independent foundation (National Evaluation of Applications of Drugs, LABAG), which is appointed by the health insurance companies and comprises representatives of dermatologists, health insurance companies and government.[2] The number of applications in 2005 and 2006 were 773 and 934, respectively, of which 51% were first applications in the last year. A few years after the introduction of this reimbursement system, we wished to evaluate its use and more specifically the reimbursement criteria among its users.

Table 1. National reimbursement criteria for biologicals in psoriasis in several European countries

	Denmark	France	Germany	Italy	Netherlands	Norway	U.K.
Disease severity	PASI>10 or BSA>10 or DLQI>10	Severe plaque psoriasis	Moderate to severe psoriasis	Moderate to severe psoriasis	PASI>10 or PASI>8 and Skindex>35	Moderate to severe psoriasis	PASI≥10 and DLQI>10
PUVA/UVB	PUVA or UVB 3x/wk ≥ 8-10 wks[a]	Yes[b]	Yes	Yes	PUVA or UVB 2x/wk 10 wks	PUVA or UVB[c]	Yes
Methotrexate	15-20mg/wk for ≥ 3 months	Yes[b]	Yes	Yes	22.5 mg/wk 3 months	Yes[c]	Yes
Ciclosporin	2.5-5 mg/kg/day ≥ 3 months[d]	Yes[b]	Yes	Yes	2.5-5 mg/kg/day 3 months	Yes[c]	Yes
Acitretin	25-50 mg/day for ≥ 3 months[d]	No	No, instead fumaric acid esters	Yes	No	No	No

PASI, Psoriasis Area and Severity Index; BSA, percentage body surface area involved; DLQI, Dermatology Life Quality Index; PUVA, psoralen plus ultraviolet (UV) A.

[a]Patients who need more than one PUVA or two UVB treatments a year or have received more than 150–200 PUVA treatments are also defined as nonresponsive patients.

[b]Failure of at least two of these treatments.

[c]Failure of one of these therapies.

[d]Ciclosporin or acitretin are required only if a patient has contraindications to methotrexate.

Between February 2007 and June 2007, a detailed, anonymous, postal survey was conducted among all members of the Dutch Society of Dermatology and Venereology. After an announcement letter, two questionnaires, reminder letters, and a final announcement at the national meeting, the database was closed. Responders did not receive any payment.

Of the 353 eligible dermatologists, 46% completed the questionnaire, of whom 63% were men, 35% were aged 44 years or younger, 37% were between 45 and 54 years and 27% were 55 years or older, and 80% practised in a nonuniversity hospital. For age and gender, there were no significant differences between responders and nonresponders (data not shown). Twenty-eight per cent reported that they had never prescribed biologicals, 56% had treated one to nine patients and 15% had treated 10 or more patients with a biological.

Almost 70% of the participants rated their knowledge of the Dutch reimbursement criteria as good to excellent. Although 78% of the dermatologists agreed with the introduction of reimbursement criteria, 75% found them inconvenient, especially the ciclosporin and methotrexate criteria (54% and 45%, respectively). Forty per cent of the responders claimed to adhere to the criteria, but also 40% admitted overestimating the Psoriasis Area and Severity Index (PASI) calculation, methotrexate dosage, and intolerance to methotrexate and ciclosporin. Alternative routes, such as entering in clinical trials or referral to a rheumatologist, were used by about 45% of dermatologists to administer biologicals to patients who were otherwise not eligible.

Figure 1 illustrates, for each (detail of) criterion, the answer of the dermatologists who were asked to indicate whether they would maintain, adjust (i.e. make it more or less strict) or exclude it. More than two-thirds of the responders agreed with PASI > 10 and failure of photo(chemo) therapy. Although 59% of the participants accepted prior methotrexate use, the dosing of 22.5 mg weekly was considered too stringent by 83%. About 70% of the dermatologists would exclude failure of ciclosporin. A quarter of the dermatologists confirmed that failure of UVB/

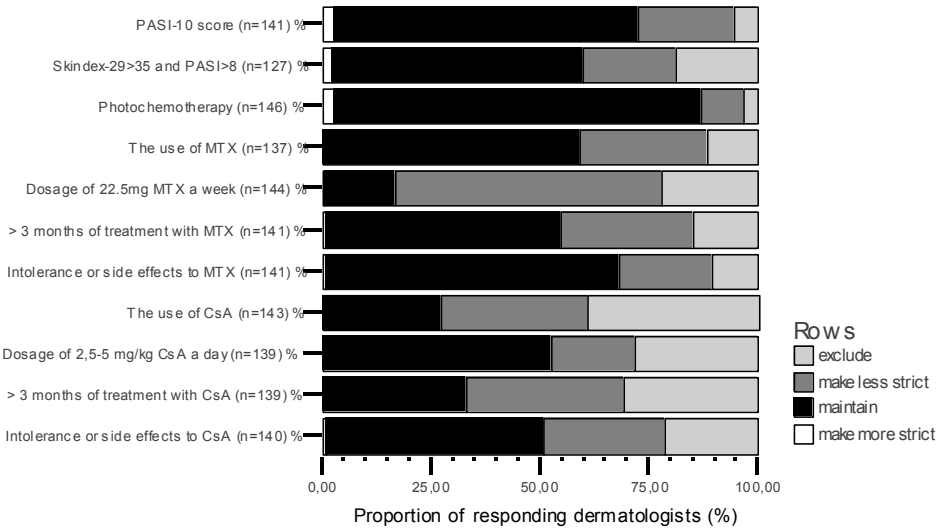

Figure 1. Distribution of the opinion of dermatologists on the Dutch reimbursement criteria. PASI, Psoriasis Area and Severity Index; MTX, methotrexate; CsA, ciclosporin.

PUVA and methotrexate and ciclosporin were the preferred criteria, 37% preferred failure of UVB/PUVA and methotrexate or ciclosporin and the remaining suggested even less stringent criteria.

The findings of this Dutch survey suggest that failure to respond to UVB or PUVA, and methotrexate or ciclosporin, are preferable as reimbursement criteria. The preference to exclude ciclosporin as a criterion by about 70% of the responders may be explained by its risk/benefit profile, skin cancer-promoting interaction with photo(chemo)therapy, national tradition and/or the observation that only a minority of dermatologists is comfortable using both methotrexate and ciclosporin in the treatment of psoriasis.[3] Also, from a patient safety perspective it is not ideal to acquire high doses of exposure to all psoriasis treatments because of interactions. Both UV and ciclosporin exposure are strong iatrogenic risk factors for the development of squamous cell carcinoma (SCC).[4-7] The skin cancer risk increases exponentially after 250 PUVA or 300 UVB treatments.[5] In the 'PUVA follow up study', a synergy was demonstrated between PUVA and subsequent ciclosporin use in the development of SCC probably due to a decreased cutaneous immune surveillance.[6]

This is the first national survey that evaluates the reimbursement criteria for biological therapies, and the results may differ between countries. Despite multiple attempts to maximize the response rate, only 46% of the invited dermatologists participated. Unfortunately, we were unable to compare responders and nonresponders, except for age and gender. However, it is likely that the majority of the dermatologists interested in the management of severe psoriasis responded because of the specific content of the questionnaire and that at least one dermatologists from each of the about 130 Dutch dermatology partnerships participated.

The findings of this survey, and the long-term safety data of the conventional therapies, may stimulate a debate about the current reimbursement criteria, especially the required failure to respond to ciclosporin.

Acknowledgments

We thank all participating dermatologists. This survey was conducted with an unrestricted grant from Merck-Serono, Schering-Plough and Wyeth.

References

1. EMEA Committee for Proprietary Medicinal Products (CPMP). Note for Guidance on Clinical Investigation of Medicinal Products Indicated for the Treatment of Psoriasis. CPMP/EWP/2454/02. London: EMEA, 2004.
2. LABAG. Landelijk beoordelingsinstituut voor aanvragen groeihormoon en biologicals voor reumatologische en dermatologische indicaties. Home page at http://www.labag.nl/ (last accessed 13 January 2008).
3. Nijsten T, Lambert J. Dermatologists' views and opinions about photo(chemo)therapy and conventional systemic psoriasis therapies: results from a Belgian survey. Dermatology 2006;213(2):123-33.
4. Nijsten TE, Stern RS. The increased risk of skin cancer is persistent after discontinuation of psoralen+ultraviolet A: a cohort study. J Invest Dermatol 2003;121(2):252-8.
5. Lim JL, Stern RS. High levels of ultraviolet B exposure increase the risk of non-melanoma skin cancer in psoralen and ultraviolet A-treated patients. J Invest Dermatol 2005;124(3):505-13.
6. Marcil I, Stern RS. Squamous-cell cancer of the skin in patients given PUVA and ciclosporin: nested cohort crossover study. Lancet 2001;358(9287):1042-5.
7. Paul CF, Ho VC, McGeown C, et al. Risk of malignancies in psoriasis patients treated with cyclosporine: a 5 y cohort study. J Invest Dermatol 2003;120(2):211-6.

Chapter 10

Psocare: Italy Shows the Way in Postmarketing Studies

T. Nijsten
M. Wakkee

Dermatology. 2008;217(4):362-4.

Editorial for: Impact of body mass index and obesity on clinical response to systemic treatment for psoriasis. Evidence from the psocare project.

Psocare

In this issue of *Dermatology* , the first of likely many studies using data from Psocare is published.[1] Psocare is an Italian group of dermatologists, psoriasis patients, epidemiologists and drug safety experts that proactively study pharmacovigiliance by linking drug prescription data to information on treatment outcome such as effectiveness and (long-term) safety.[2] This programme is part of the regional health authorities that appoint reference centres for the treatment of moderate to severe psoriasis and is funded by the Italian Medicine Agency (AIFA). Each of the 140 reference centres participated in Psocare in part because registration is mandatory to administer conventional and new systemic psoriasis therapies. At standardized follow-ups, demographic and lifestyle characteristics, treatment exposure, psoriasis severity and any medical event (i.e. new diagnoses, hospitalizations, outpatient specialist visits) are ascertained. Psocare started in September 2005. In 18 months, the Psocare database included >8,000 patients that received a systemic therapy for the first time, illustrating the successfulness of this nationwide collaboration.

In addition to Psocare, the Italians initiated the development of an international registry, which is called Psonet.[3] The goal of Psonet is to establish a network of independent European population-based registries that will perform coordinated postmarketing surveillance studies to monitor the effectiveness and safety of systemic agents, including biologics, in the treatment of psoriasis. Accordingly, international data can be pooled to reach sufficient power and new drugs can be easily monitored in the future. Established registries try to link to Psonet and new ones are under construction to use the Psocare framework to collect a standardized 'core set' of variables. The countries that participate include Italy, France, Israel, Portugal, Spain, Sweden, the Netherlands and the UK. Moreover, the establishment of a multidisciplinary and international group of investigators sharing resources and activities may increase the quality of (pharmaco) epidemiological studies and stimulate the development of independent pragmatic randomized controlled trials (RCT) that are needed by patients and physicians.[4, 5]

In our opinion, Psocare and Psonet may revolutionize postmarketing and pharmacoepidemiological studies in and outside dermatology. The manufacturers of the psoriasis drugs should have studied several aims of the these frameworks, but a recent Food and Drug Administration survey showed that only 34% of 2,701 postmarketing commitments were honoured.[5, 6] No such data are available for the European Medicines Agency. Since there is a lack of information about drug behaviour outside the restricted clinical trial population, commercially less interesting (hard) outcomes and long-term safety of drugs, the AIFA has established a programme to fund independent research that focuses on clinical studies that assess orphan drugs, head-to-head comparisons and pharmacoepidemiology.[7] An innovative aspect of this programme is its funding: an ad hoc fund was set up, requiring pharmaceutical companies to contribute 5% of

their annual budget devoted to their physician-aimed promotional activities. An independent scientific committee reviews the grant applications and distributes about EUR 40 million annually. This Italian initiative may also serve as an example for other countries or, referably, the European Union.[5]

Efficacy versus Effectiveness

Clinical studies report the efficacy of therapies under 'ideal' circumstances. The study patients are selected according to strict in- and exclusion criteria, are motivated to use a (new) drug and are intensely monitored. More difficult patients to treat such as elderly, children, those with important co-morbidities or history of cancer, treatment-resistant disease, increased alcohol consumption and history of poor adherence are commonly excluded from clinical trials. The effectiveness of a therapy is its benefit when it is applied after approval in large heterogeneous populations in real life. In this issue of Dermatology, the Psocare study group reports the effectiveness of systemic psoriasis therapy after 16 weeks.[1] The proportion of biological users is high because 'incident therapy' patients were included and people with a treatment history (of course, most often conventional treatments) were not excluded for the follow-up of that specific therapy. The proportion of patients achieving a 75% reduction in the Psoriasis Area and Severity Index (PASI-75) of the conventional and biological therapies varied between 38 and 63% for acitretin and infliximab, respectively, but generally the effectiveness was about 50%. For most therapies in this population-based study, the effectiveness was considerably lower than the efficacy reached in RCT.[8] This may be due to a different study population (as mentioned above), less placebo effect and/or 'eligibility creep'.[9, 10] Interestingly, after 16 weeks of efalizumab, 142 of 295 Italian patients (48%) achieved PASI-75, which is considerably higher than 28% in large approval RCT.[11] The explanation of this 'positive' difference is unclear but may be related to patients and disease characteristics and/or pharmacogenetics.

Obesity and Psoriasis

Multiple observational studies have demonstrated a significant positive association between adiposity and psoriasis; psoriasis patients are more likely to have a higher body mass index (BMI) than controls.[12-14] However, the directionality of this relationship is not clear. Are psoriasis patients more obese because they have a different lifestyle (e.g. different eating habits, consume more alcohol and exercise less due to an impaired health-related quality of life) or does the chronic low-grade inflammatory state in obesity induce psoriasis? Some epidemiological studies suggest that obesity precedes psoriasis, while another investigation found that it appeared after the onset of psoriasis.[12, 15, 16] Recently, the first prospective cohort on

the interaction between adiposity and the incidence of psoriasis showed a strong, consistent dose-response relationship. However, large populationbased prospective cohort studies on the natural course of psoriasis as well as randomized clinical trials investigating the effect of weight reduction on psoriasis severity are lacking.[14]

Does BMI Predict Treatment Response?

In dermatology, relatively few studies have investigated the effect of demographic, lifestyle and disease characteristics on treatment response. In this issue of Dermatology, Naldi et al.[1] show that obesity is an independent predictor of treatment outcome in psoriasis. After 16 weeks of therapy, 59% of the patients with a BMI <20 and 42.4% of those with a BMI>30 achieved a PASI-75 reduction. Of the patients with a value between 20 and 30, about 52% responded well to therapy. Compared to subjects with a BMI between 20 and 24, those with an index >30 were about 40% less likely to show a good treatment response. For cyclosporine, efalizumab and etanercept, nonobese patients (BMI <30) were significantly more likely to achieve PASI-75 than those with a BMI >30 at week 16. No significant differences between the 2 groups were observed for acitretin, infliximab, methotrexate and psoralen and UVA. Although obese patients seemed to be less responsive to each of the treatments, no significant variation was documented after 8 weeks.

In the Utah Psoriasis Initiative, obesity did not impact the response to methotrexate, psoralen and UVA and corticosteroids among 557 participants.[16] In 1,651 clinical trial patients, the BMI did not significantly affect the efficacy of efalizumab, but the intermediate groupshowed a 'nominally higher response rate' than those with values ≥35 and <25.[11] The BMI did not influence the effectiveness of the fixed-dose biologic etanercept in a small group of patients.[17] In agreement with psoriasis, the impact of obesity on treatment response in patients with rheumatoid arthritis, who have an inflammatory state comparable to those with psoriasis, is controversial.[18, 19]

The association between BMI and treatment response is complex because it may be confounded by many variables. For example, smoking, alcohol consumption and treatment adherence may be associated with both obesity and outcome. Somewhat surprisingly, in the Psocare study, no significant differences between the obese and nonobese patients were detected for age, gender, smoking habits, alcohol consumption, psoriasis severity and treatment history, suggesting that the association between BMI and treatment response was independent of these factors. However, other aspects that were not included in the analyses may have affected the findings of this study. For example, treatment adherence is associated with obesity (i.e. more

obese patients are less likely to take their drugs as prescribed) and surely negatively impacts the effectiveness of therapy.[20]

In conclusion, Psocare is a gigantic step forward in postmarketing evaluations of psoriasis therapies. Hopefully, this initiative is followed by other national and international agencies such as the European Medicines Agency. The first finding of Psocare is that the BMI may predict the treatment outcome in psoriasis patients, suggesting that obesity should be taken into account in RCT and clinical practice. Additional studies on psoriasis such as RCT that assess weight reduction are needed to further explore the association between obesity and psoriasis.

References

1. Naldi L, Addis A, Chatenoud L, et al. Impact of body mass index and obesity on clinical response to systemic treatment for psoriasis. Evidence from the psocare project. Dermatology 2008.
2. Psocare. http://www.psocare.it/cms/home_eng (accessed January 11, 2007).
3. Psonet. http://www.psonet.eu/ (accessedJanuary 11, 2007).
4. Remuzzi G, Schieppati A, Boissel JP, Garattini S, Horton R. Independent clinical research in Europe. Lancet 2004;364(9446):1723-6.
5. Garattini S, Bertele V. How can we regulate medicines better? BMI 2007;335(7624):803-5.
6. Stern RS, Nijsten T. Insuring rapid and robust safety assessment. J Invest Dermatol 2004;122(3):857-8.
7. Agenzia Italiana del Farmaco. http://www.agenziafarmaco.it./wscs_render_attachment_by_id/tipo_file0109.pdf (accessed January 11, 2007).
8. Stern RS. A promising step forward in psoriasis therapy. Jama 2003;290(23):3133-5.
9. Spuls PI, Witkamp L, Bossuyt PM, Bos JD. The course of chronic plaque-type psoriasis in placebo groups of randomized controlled studies. Arch Dermatol 2004;140(3):338-44.
10. Hick J, Feldman SR. Eligibility creep: a cause for placebo group improvement in controlled trials of psoriasis treatments. J Am Acad Dermatol 2007;57(6):972-6.
11. Pariser DM, Gordon KB, Papp KA, et al. Clinical efficacy of efalizumab in patients with chronic plaque psoriasis: results from three randomized placebo-controlled Phase III trials: part I. J Cutan Med Surg 2005;9(6):303-12.
12. Naldi L, Chatenoud L, Linder D, et al. Cigarette smoking, body mass index, and stressful life events as risk factors for psoriasis: results from an Italian case-control study. J Invest Dermatol 2005;125(1):61-7.
13. McGowan JW, Pearce DJ, Chen J, Richmond D, Balkrishnan R, Feldman SR. The skinny on psoriasis and obesity. Arch Dermatol 2005;141(12):1601-2.
14. Setty AR, Curhan G, Choi HK. Obesity, waist circumference, weight change, and the risk of psoriasis in women: Nurses' Health Study II. Arch Intern Med 2007;167(15):1670-5.
15. Mallbris L, Larsson P, Bergqvist S, Vingard E, Granath F, Stahle M. Psoriasis phenotype at disease onset: clinical characterization of 400 adult cases. J Invest Dermatol 2005;124(3):499-504.
16. Herron MD, Hinckley M, Hoffman MS, et al. Impact of obesity and smoking on psoriasis presentation and management. Arch Dermatol 2005;141(12):1527-34.
17. de Groot M, Appelman M, Spuls PI, de Rie MA, Bos JD. Initial experience with routine administration of etanercept in psoriasis. Br J Dermatol 2006;155(4):808-14.
18. Hoekstra M, van Ede AE, Haagsma CJ, et al. Factors associated with toxicity, final dose, and efficacy of methotrexate in patients with rheumatoid arthritis. Ann Rheum Dis 2003;62(5):423-6.
19. Kent PD, Luthra HS, Michet C, Jr. Risk factors for methotrexate-induced abnormal laboratory monitoring results in patients with rheumatoid arthritis. J Rheumatol 2004;31(9):1727-31.
20. Schrott HG, Bittner V, Vittinghoff E, Herrington DM, Hulley S. Adherence to National Cholesterol Education Program Treatment goals in postmenopausal women with heart disease. The Heart and Estrogen/Progestin Replacement Study (HERS). The HERS Research Group. JAMA 1997;277(16):1281-6.

Chapter 11

General discussion and perspectives

11.1 Comorbidity in psoriasis patients

Most research on comorbidities in dermatological diseases has been conducted among patients with psoriasis.[1, 2] The number of diseases that are thought to be associated with psoriasis is substantial and have expanded significantly in the last years (Table 1). Most research is based on observational studies using secondary databases, which are ideal for generating hypotheses, but are limited in their ability to clearly differentiate between association and causality.

Table 1. Comorbidities that have been associated with psoriasis.

Comorbidities
Psoriatic arthritis[3]
Cardiovascular diseases[4-6]
- diabetes mellitus
- hypertension
- hyperlipidaemia
- atherosclerosis
- angina
- myocardial infarction
- peripheral vascular diseases
- stroke
Malignancies[7-11]
- nonmelanoma skin cancer
- lymphoma
- acute promyelocytic leukemia
- lung cancer
- cancer of upper aerodigestive tract
- liver cancer
- pancreas cancer
- breast cancer
- cancer of the vulva, penis, bladder
- kidney cancer
Infections[12]
Depression[13]
Osteoporosis[14]
Inflammatory bowel diseases[15, 16]
- crohn's disease
- coeliac disease
Chronic obstructive pulmonary disease[17]
Non-alcoholic fatty liver disease[18]

One of the comorbidities that has received a lot of attention in psoriasis are cardiovascular diseases. Basic research has demonstrated that in both diseases pro-inflammatory cytokines like TNF-alpha and IL-1 play an important role, which led to the hypothesis that the pro-inflammatory profile of psoriasis patients may adversely affect their cardiovascular risk profile (chapter 3). Factors that have been suggested to be unfavorably affected by this chronic inflammation are oxidative stress, endothelial function, blood pressure, blood platelet adhesion, homocysteine levels and the lipid profile accelerating the process of atherosclerosis and ultimately resulting in acute myocardial infarction (Figure 1).[19]

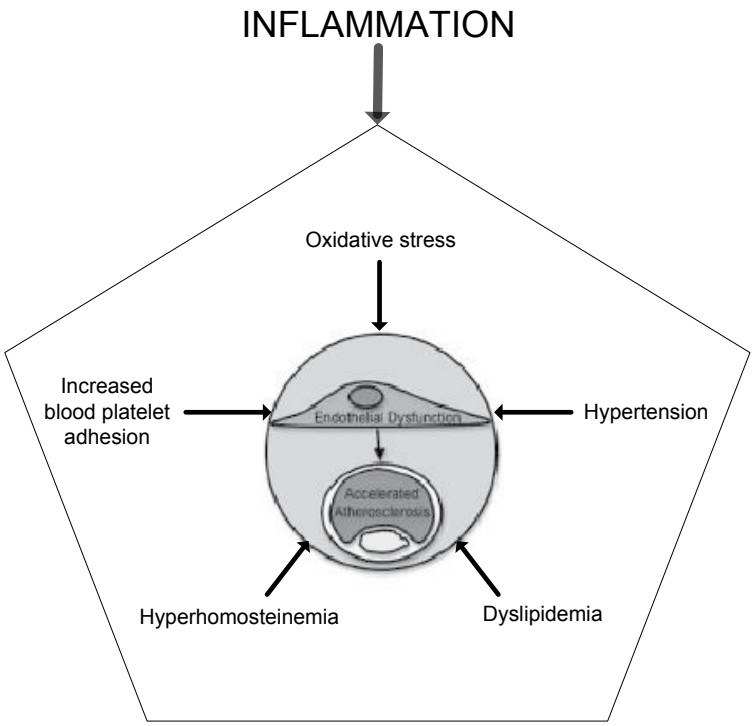

Figure 1. This figure represents the various factors that are unfavourably affected by chronic inflammation as has also been hypothesised to occur in patients with psoriasis.

Several studies have suggested that psoriasis is associated with various cardiovascular diseases such as diabetes mellitus, hypertension and dyslipidemia. Our study demonstrated the complexity of investigating these associations by exploring the prevalent use of cardiovascular and antidiabetic drugs in psoriasis patients and a matched reference cohort (chapter 5). It showed that over a five year-observation period the psoriasis population had higher prescription rates of metabolic drugs such as anti-hypertensives, anti-coagulant and anti-platelet agents, nitrates, digoxin, lipid-lowering and antidiabetic drugs compared to the reference population, but that the psoriasis population also had a higher overall use of prescription drugs. After adjusting for the total number of unique prescriptions as a proxy for the extent of healthcare consumption, none of the associations between psoriasis and metabolic drug classes remained significant, except that now more severely affected psoriasis patients used significantly less beta-blockers. The results of this study stress the impact of healthcare consumption on the detection of cardiovascular associations in patients with psoriasis compared to 'healthy' reference subjects. Increased healthcare utilization leads to detection bias, which especially affects common diseases that are frequently underdiagnosed like hypertension, dyslipidemia and diabetes mellitus. For example, a psoriasis patient consulting his/her physician for a psoriasis therapy is likely to be simultaneously screened for diseases as recommended by national guidelines

irrespective of therapy given and additionally pre-treatment screening measures may also result in detecting other diseases. The lower prescription rate of beta-blockers to patients with severe psoriasis is probably because of their increased likelihood to receive specialized care from dermatologists who are attentive of the possible negative effect of beta-blockers on the psoriasis activity.

In 2006, a landmark paper appeared by Gelfand et al. showing that patients with psoriasis had a small but significantly increased risk of myocardial infarction (MI) compared to people without psoriasis, independent of other risk factors.[5] This observational cohort study based on General Practice Research Database (GPRD) records additionally suggested that the risk of MI increased with psoriasis severity, showing an HR of 1.11 (95% CI 1.07-1.17) for MI in patients who only used topical anti-psoriatic therapies and a HR of 1.43 (95% CI 1.18-1.72) for severe psoriasis patients defined as ever receiving a systemic therapy. In this study the relative risk of MI was inversely related to age. The authors concluded with the call for additional studies to confirm their findings. Nevertheless, a trend was set in scientific literature and meeting presentations to upgrade psoriasis from a cutaneous to a systemic disease without any observational studies designed to address this hypothesis or interventional clinical trial.[20, 21] A remarkable development, especially since earlier observational studies were less clear about this association. Some only found an increased risk of MI in females and others noticed this association especially in males, while studies of cardiovascular mortality only detected higher rates among inpatients or even detected no increased cardiovascular mortality at all.[12, 22-24]

We subsequently investigated the clinically relevant outcome of hospitalization for ischemic heart disease (IHD) in a cohort of psoriasis patients and an age and gender matched reference cohort (chapter 6). Our study showed that patients from the psoriasis cohort used more drugs associated with the metabolic syndrome and were again higher healthcare consumers, but that the risk of being hospitalized for an acute IHD or MI more specifically was not significantly different and even decreased after adjusting for the use of metabolic drugs (as a proxy for the presence of other cardiovascular disease) and consumption of healthcare. Neither did we find a significantly different risk of IHD among patients with mild or more severe psoriasis, therefore rejecting a dose-response relationship between the severity of inflammation and the risk of IHD.

Our data differ from the interpretations of the results of the study performed in the GPRD by Gelfand et al[5], although the factual differences between the GPRD based study and our study are marginal. The risk of IHD tended to be increased in our study, but the analyses of our data suggest that other factors, e.g. referral bias for other disease are important for interpretation of our results. It might well be that the results that were found in the GPRD study have been biased likewise.

A recent US veterans database study again suggested the presence of more cardiovascular risk factors in patients with psoriasis and showed an association between psoriasis and coronary artery, cerebrovascular, and peripheral vascular disease after adjusting only for these traditional cardiovascular risk factors.[25] However, there have now also been some recent papers presenting other results, like the study by Brauchli et al. who also used the GPRD data but did not find an overall increased risk of incident MI in psoriasis.[26] Another study investigating pre-clinical CVD, indicated that psoriasis per se does not increase the risk of pre-clinical CVD, but that the high prevalence of confounding variables may account for the excess risk of CVD noticed in patients with psoriasis.[27] The available evidence therefore seems insufficient to position psoriasis as a systemic disease or independent risk factor for cardiovascular disease. Hopefully, the available data will lead to a critical discussion on the causal relationship between psoriasis and cardiovascular disease before early conclusions are drawn. Additionally, as has also been suggested in the editorial by Stern[28], according to the criteria used by the US Preventative Task Force to evaluate potential new risk factors (Table 2) psoriasis is neither a potential clinically useful independent risk factor for CVD.[29] The main concept of these criteria is that the new risk factor improves the prediction of CVD in addition to traditional CVD risk factors. However, there appears to be no evidence that psoriasis or even severe psoriasis is of additional prognostic value when traditional risk factors for CVD are accurately assessed among psoriasis patients. Another potential problem would also be to easily and reliably diagnose and assess the psoriasis severity especially in case of non-dermatologists. Psoriasis neither reclassifies a substantial proportion of intermediate risk persons as high risk, since any potential effect of psoriasis on the risk of MI, if this should be present, would be expected only among a small subpopulation of young psoriasis patients with severe psoriasis.[5] The fourth criterion implies that individuals who are reclassified as having a high risk of CVD by this new risk factor should receive different care than they would normally get aimed at reducing their risk of CV events. A possible protective effect has been suggested by TNF-alpha for psoriasis patients and the first trial is currently recruiting psoriasis patients to investigate the anti-inflammatory effect of etanercept

Table 2. Criteria for Evaluating the Clinical Value of a New Risk Factor

To be useful for reclassifying patients currently considered to be at intermediate risk for major CHD events, a new risk factor must meet the following criteria[29]:
1. It should be easily and reliably measured. Laboratory, radiographic, or clinical measurement should have accepted population reference values. A relatively high prevalence of abnormal values and a substantial proportion of normal values should be found among intermediate-risk persons.
2. It should be an independent predictor of major CHD events in intermediate-risk persons who have no history of coronary artery disease and no coronary equivalents, such as cerebrovascular or peripheral vascular disease.
3. When assessed in intermediate-risk persons, it should reclassify a substantial proportion of them as high-risk.
4. Reclassified individuals should be managed differently than they would have otherwise been, and new or additional treatment they receive should reduce their risk for CHD events.
5. If 2 or more risk factors provide similar prognostic information, then convenience, availability, cost, and safety may be important in choosing among them.

on CRP as a marker of the metabolic syndrome in psoriasis patients.[30] However, using CRP level as a primary outcome measure is controversial since it may only be increased among severe psoriasis patients and Buckley et al recently also described that the evidence for reducing CRP levels to prevent coronary heart diseases is lacking.[31] Furthermore, it was shown that TNF-alpha inhibitors lower homocysteine levels among psoriatic arthritis patients, but long-term studies with TNF-alpha blockade showed weight gain and long term use in RA patients also led to a pro-atherogenic effect by increased triglyceride and Apo-B levels. It would therefore be difficult to assess the net effect of TNF-alpha the CV profile of psoriasis patients. In section 13.2 we will further discuss how these data also affect the trends in treating psoriasis patients.

The previously mentioned studies confirm that studying comorbidities in psoriasis patients is complex and requires careful data interpretation in particular before additional interventions are suggested. Although the presence of chronic inflammation has often been hypothesized as the direct link between psoriasis and various comorbidities, several other factors are likely to play important roles and confound the detected associations as presented in Figure 2 (chapter 7). First, psoriasis has a major impact on the health related quality of life (HRQOL), which may lead to an unhealthy lifestyle that includes smoking, excessive alcohol consump-

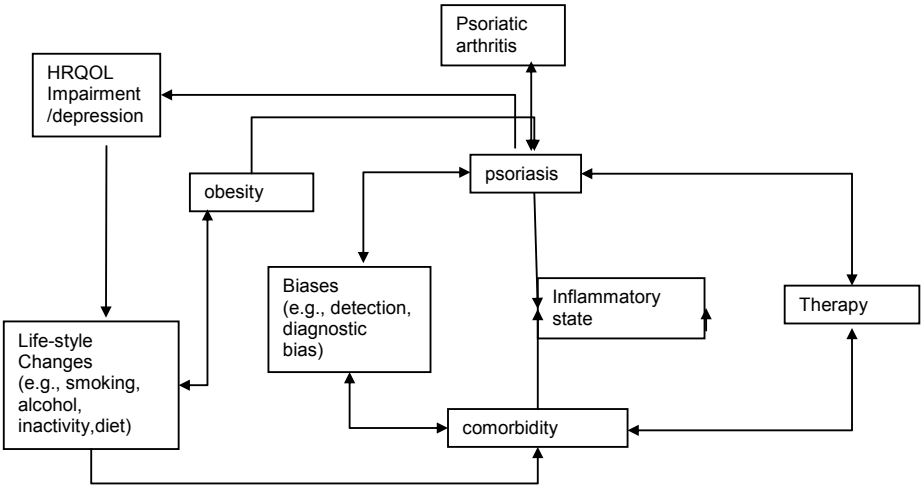

Figure 2. Schematic overview of possible factors influencing the association between psoriasis and comorbidities.

tion, decreased physical activity and obesity. These are independent risk factors for diseases such as cardiovascular diseases, infections, malignancies, but interestingly excessive body weight is also suggested as a risk factor for the onset of plaque psoriasis and higher psoriasis activity.[32, 33] Secondly, the use of various systemic anti-psoriatic therapies may also increase the risk of several comorbidities (e.g. UV therapy and non-melanoma skin cancer, cyclosporine and

hypertension). The final confounder is the effect of detection bias, which has been confirmed in our studies. Psoriasis patients are more likely to visit a physician because of their disease, which also increases their likelihood of screening and the detection of other comorbid conditions that may have been missed otherwise. Additionally, psoriasis patients that seek medical care for their psoriasis, although the majority has limited disease, are also more likely to visit a physician for other conditions. Unfortunately, secondary database studies rarely have complete information about all relevant confounders. We therefore believe that residual confounding has affected the detection of comorbidities that have been suggested to be associated with psoriasis (Table 1). Of course observational study designs are prefect for generating hypotheses on possible associations, but do not allow clear differentiation between association and causality. The ultimate goal to study causality between psoriasis and other diseases would be to conduct large prospective cohort studies on incident psoriasis patients that include information on all relevant confounders or conduct a randomized clinical trial with CVD as primary outcome in treated and untreated psoriasis patients.

This thesis also investigated the interesting and relevant association between psoriasis and infections. A recent study in Nature Genetics found that psoriasis patients produced significantly more antimicrobial peptides, although the potential clinical relevance of a protective effect against infections has not been determined.[34] Together with the ongoing concern about the elevated risk of serious infectious diseases due to immunosuppressive drugs including biologicals, it was pivotal for us to assess the baseline risk of infectious diseases in psoriasis patients.[34-36] Up until now, the few studies that have examined the risk of serious infections in patients with psoriasis suggest that psoriasis patients may have a higher risk of viral infections, pneumonia and sepsis. Our population based cohort study, which focussed on serious infections that required patients to be hospitalized, confirmed previous findings and showed that the risk of all major serious infectious diseases (IDs) was higher in patients with psoriasis compared to controls and highest in those with more severe psoriasis (chapter 6). This association was partly explained by confounding by higher prevalence of comorbidities such as diabetes and COPD, although it remained significant after adjusting. Remarkably, we were not able to confirm an association between the occurrence of IDs and recent systemic drug prescriptions, which one might expect to find because of immunosuppressive effects of systemic drugs. In this study, the effect of detection bias was likely to be smaller compared to prior studies because patients with severe infections are likely to consult a physician.

11.2 The treatment of psoriasis patients

Approximately ten years ago the first studies appeared on the significant negative impact of psoriasis on the patients' quality of life compared with other chronic medical conditions.[33]

Additionally it was shown that psoriasis is also associated with a depressive symptoms in a relatively large proportion of patients.[37, 38] As a result, dermatologists learned there was a greater need for intervention and that psoriasis patients may have been undertreated based on the idea that psoriasis was merely a cosmetic problem (Figure 3). This has led to incorporating the impact of psoriasis on the HRQOL in the current psoriasis treatment guidelines and has lowered the threshold for starting a systemic therapy including biologics.[39]

This trend now seems ongoing from psoriasis as a disease that has a significant impact on the HRQOL, to a systemic disease (Figure 3). Some recent papers therefore already suggest even more aggressive treatment of psoriasis to prevent comorbidities, which may be potential 'systemic' consequences of psoriasis.[20, 21] At a recent expert meeting the concept of cardioprotection via anti-inflammatory medications led to agreement among many panelists that TNF-inhibitors should be considered as a first option when treating obese patients because of the potential cardioprotective effects and overall efficacy associated with these agents.[30] This is a remarkable statement since there is no substantial evidence for the added value of more aggressive treatment of psoriasis to prevent for example CV comorbidities and as we discussed earlier TNF-alpha can even increase the BMI and may have other unfavorable cardiovascular effects.

This ongoing trend attempts to position psoriasis as a serious disease within the spectrum of chronic illnesses and can also be utilized to affect the allocation of industrial and governmental resources on research within this field. Hopefully, this thesis helps to obtain a balanced view on

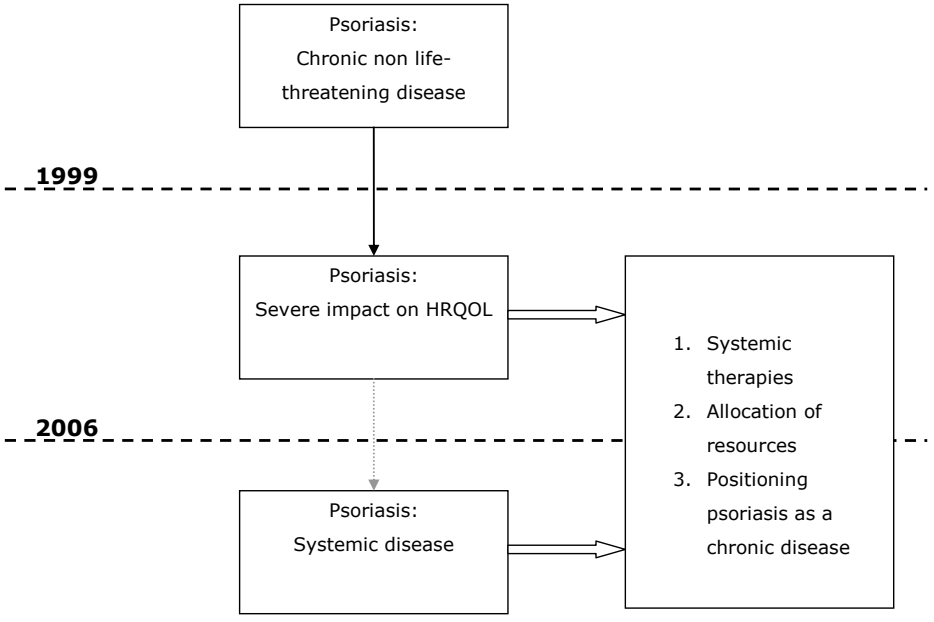

Figure 3. Developments in the treatment of psoriasis.

the existence and cause of various comorbidities, the complexity of studying these associations and their potential clinical impact.

Independent of the cause of potential comorbidities, their presence can affect treatment response and safety as well as reduce the therapeutic possibilities for psoriasis due to contra-indications for systemic therapies (chapter 10). A postmarketing effectiveness and safety study has shown that obesity for example may negatively affect treatment outcome in psoriasis patients.[40] Since clinical studies report treatment efficacy among an 'ideal' homogeneous patient group, postmarketing studies are pivotal to describe how demographic, lifestyle and disease characteristics affect treatment response in the real world. To accurately determine the safety of drugs, short and long term drug safety data are need as well as a baseline risk of various comorbidities in patients with psoriasis. These results may subsequently be incorporated into guidelines to advice healthcare providers on the baseline risk of comorbidities in patients with psoriasis, the treatment possibilities and expected treatment effect in psoriasis patients with comorbidities.

Since 2003, the prescription of systemic therapies including photo(chemo)therapy has been supported by the national practice guidelines for the treatment of severe chronic plaque-type psoriasis in the Netherlands. Evaluation of its implementation among a large sample of Dutch dermatologists showed that almost all dermatologists were aware of the existence of these guidelines and a large proportion also new about the chapter on biological therapies that was added in 2005 (chapter 8). Good knowledge of the guidelines were reported by 60%. The dermatologists' views on the guidelines were generally positive, although there was some disagreement on the user-friendliness and communication facilitating properties. Increasing familiarity with the guidelines was a significant predictor for a more positive attitude towards them. Three-quarters of the participating dermatologists used the reported guidelines in daily practice and its use was highest among dermatologists with larger psoriasis populations and those with good familiarity of the guidelines. Increasing the dermatologists' familiarity may therefore lead to a more positive view and more frequent use of the guidelines.

This survey also evaluated the reimbursement criteria for biological therapies for psoriasis in the Netherlands. In the Netherlands biological therapies were only reimbursed among patients with moderate to severe psoriasis who are unresponsive, intolerant or have contraindications for PUVA, methotrexate and cyclosporine, while in some European countries (e.g. Denmark, France and Norway) biologics are reimbursed after failure of one or two systemic therapies. Three-quarter of the responding dermatologists agreed with the introduction of reimbursement criteria, but a comparable proportion also though the current criteria were too strict. The findings of this survey suggested that failure to respond to UVB or PUVA, and methotrexate or cyclosporine are preferable as reimbursement criteria. Based on these survey outcomes

combined with the cumulative skin cancer inducing effects of UV and cyclosporine, the working group of inflammatory diseases of the Dutch Society of Dermatology and Venereology has changed the indications for the treatment of moderate to severe chronic plaque psoriasis in the current national guidelines to UV and methotrexate or cyclosporine and have requested the minister of health to change the reimbursement criteria as well (www.huidarts.info/news). On request of the manufacturers of etanercept, the Health Care Insurance Board is currently considering to adapt the changed guidelines, but this may require additional health economic studies to estimate the financial impact of liberalizing the reimbursement criteria of biologicals in the therapy of psoriasis.

11.3 Future perspectives

Comorbidities have emerged in dermatology and especially in the field of psoriasis. Their potential etiological, preventative and therapeutic relevance will likely lead to much more comorbidity studies, meetings en publications. Hopefully, future views on comorbidities in psoriasis will be balanced and incorporate the complex nature of studying associations before causal relationships are assumed. Ideally, new data on comorbidities will arise from large prospective studies of new psoriasis patients in which data on all potential confounders are collected.

In the future, new treatments including biologics will be developed for treating psoriasis. For both new and existing systemic therapies it would be useful if also dermatologists in the Netherlands will become involved in the international registry of systemic therapies. This will increase our knowledge on postmarketing effectiveness and safety of various therapies especially in case of certain comorbidities or lifestyle factors. Additionally, useful outcomes may also be incorporated into the guidelines for the treatment of psoriasis. Finally, as far as the reimbursement of biological therapies is concerned, hopefully in the very near future the adapted criteria for reimbursement will be accepted by the minister of health.

References

1. Christophers E. Comorbidities in psoriasis. Clin Dermatol 2007;25(6):529-34.
2. Wakkee M, Nijsten T. Comorbidities in dermatology. Dermatol Clin 2009;27(2):137-47, vi.
3. Gelfand JM, Gladman DD, Mease PJ, et al. Epidemiology of psoriatic arthritis in the population of the United States. J Am Acad Dermatol 2005;53(4):573-7.
4. Kaye JA, Li L, Jick SS. Incidence of risk factors for myocardial infarction and other vascular diseases in patients with psoriasis. Br J Dermatol 2008.
5. Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB. Risk of myocardial infarction in patients with psoriasis. Jama 2006;296(14):1735-41.
6. Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB, Gelfand JM. Prevalence of cardiovascular risk factors in patients with psoriasis. J Am Acad Dermatol 2006;55(5):829-35.
7. Margolis D, Bilker W, Hennessy S, Vittorio C, Santanna J, Strom BL. The risk of malignancy associated with psoriasis. Arch Dermatol 2001;137(6):778-83.
8. Frentz G, Olsen JH. Malignant tumours and psoriasis: a follow-up study. Br J Dermatol 1999;140(2):237-42.
9. Boffetta P, Gridley G, Lindelof B. Cancer risk in a population-based cohort of patients hospitalized for psoriasis in Sweden. J Invest Dermatol 2001;117(6):1531-7.
10. Au WY, Yeung CK. Acute promyelocytic leukemia in patients with severe psoriasis vulgaris. Leuk Res 2009;33(11):e189-90.
11. Ji J, Shu X, Sundquist K, Sundquist J, Hemminki K. Cancer risk in hospitalised psoriasis patients: a follow-up study in Sweden. Br J Cancer 2009;100(9):1499-502.
12. Lindegard B. Diseases associated with psoriasis in a general population of 159,200 middle-aged, urban, native Swedes. Dermatologica 1986;172(6):298-304.
13. Van Voorhees AS, Fried R. Depression and quality of life in psoriasis. Postgrad Med 2009;121(4):154-61.
14. Dreiher J, Weitzman D, Cohen AD. Psoriasis and osteoporosis: a sex-specific association? J Invest Dermatol 2009;129(7):1643-9.
15. Lee FI, Bellary SV, Francis C. Increased occurrence of psoriasis in patients with Crohn's disease and their relatives. Am J Gastroenterol 1990;85(8):962-3.
16. Birkenfeld S, Dreiher J, Weitzman D, Cohen AD. Coeliac disease associated with psoriasis. Br J Dermatol 2009.
17. Dreiher J, Weitzman D, Shapiro J, Davidovici B, Cohen AD. Psoriasis and chronic obstructive pulmonary disease: a case-control study. Br J Dermatol 2008;159(4):956-60.
18. Gisondi P, Targher G, Zoppini G, Girolomoni G. Non-alcoholic fatty liver disease in patients with chronic plaque psoriasis. J Hepatol 2009;51(4):758-64.
19. Wakkee M, Thio HB, Prens EP, Sijbrands EJ, Neumann HA. Unfavorable cardiovascular risk profiles in untreated and treated psoriasis patients. Atherosclerosis 2007;190(1):1-9.
20. Friedewald VE, Cather JC, Gelfand JM, et al. AJC editor's consensus: psoriasis and coronary artery disease. Am J Cardiol 2008;102(12):1631-43.
21. Alexandroff AB, Pauriah M, Camp RD, Lang CC, Struthers AD, Armstrong DJ. More than skin deep: atherosclerosis as a systemic manifestation of psoriasis. Br J Dermatol 2009;161(1):1-7.
22. McDonald CJ, Calabresi P. Occlusive vascular disease in psoriatic patients. N Engl J Med 1973;288(17):912.
23. Mallbris L, Akre O, Granath F, et al. Increased risk for cardiovascular mortality in psoriasis inpatients but not in outpatients. Eur J Epidemiol 2004;19(3):225-30.

24. Stern RS, Lange R. Cardiovascular disease, cancer, and cause of death in patients with psoriasis: 10 years prospective experience in a cohort of 1,380 patients. J Invest Dermatol 1988;91(3):197-201.
25. Prodanovich S, Kirsner RS, Kravetz JD, Ma F, Martinez L, Federman DG. Association of psoriasis with coronary artery, cerebrovascular, and peripheral vascular diseases and mortality. Arch Dermatol 2009;145(6):700-3.
26. Brauchli YB, Jick SS, Miret M, Meier CR. Psoriasis and risk of incident myocardial infarction, stroke or transient ischaemic attack: an inception cohort study with a nested case-control analysis. Br J Dermatol 2009;160(5):1048-56.
27. Martyn-Simmons C, Ranawaka RR, Crook MA, et al. A prospective case-controlled cohort study to assess pre-clinical cardiovascular disease in patients with moderate to severe psoriasis. J Invest Dermatol 2009;129(Supplement 2):S30.
28. Stern RS. Psoriasis is not a Useful Independent Risk Factor for Cardiovascular Disease. J Invest Dermatol 2009 submitted.
29. Helfand M, Buckley DI, Freeman M, et al. Emerging risk factors for coronary heart disease: a summary of systematic reviews conducted for the U.S. Preventive Services Task Force. Ann Intern Med 2009;151(7):496-507.
30. Strober B, Berger E, Cather J, et al. A series of critically challenging case scenarios in moderate to severe psoriasis: a Delphi consensus approach. J Am Acad Dermatol 2009;61(1 Suppl 1):S1-S46.
31. Buckley DI, Fu R, Freeman M, Rogers K, Helfand M. C-reactive protein as a risk factor for coronary heart disease: a systematic review and meta-analyses for the U.S. Preventive Services Task Force. Ann Intern Med 2009;151(7):483-95.
32. Wolk K, Mallbris L, Larsson P, Rosenblad A, Vingard E, Stahle M. Excessive body weight and smoking associates with a high risk of onset of plaque psoriasis. Acta Derm Venereol 2009;89(5):492-7.
33. Setty AR, Curhan G, Choi HK. Obesity, waist circumference, weight change, and the risk of psoriasis in women: Nurses' Health Study II. Arch Intern Med 2007;167(15):1670-5.
34. Hollox EJ, Huffmeier U, Zeeuwen PL, et al. Psoriasis is associated with increased beta-defensin genomic copy number. Nat Genet 2008;40(1):23-5.
35. Doherty SD, Van Voorhees A, Lebwohl MG, et al. National Psoriasis Foundation consensus statement on screening for latent tuberculosis infection in patients with psoriasis treated with systemic and biologic agents. J Am Acad Dermatol 2008;59(2):209-17.
36. Kimball AB, Gladman D, Gelfand JM, et al. National Psoriasis Foundation clinical consensus on psoriasis comorbidities and recommendations for screening. J Am Acad Dermatol 2008;58(6):1031-42.
37. Rapp SR, Feldman SR, Exum ML, Fleischer AB, Jr., Reboussin DM. Psoriasis causes as much disability as other major medical diseases. J Am Acad Dermatol 1999;41(3 Pt 1):401-7.
38. Stern RS, Nijsten T, Feldman SR, Margolis DJ, Rolstad T. Psoriasis is common, carries a substantial burden even when not extensive, and is associated with widespread treatment dissatisfaction. J Investig Dermatol Symp Proc 2004;9(2):136-9.
39. CBO. Nederlandse Verenigung voor Dermatologie en Venerologie (NVDV) and Institute for Healthcare Improvement (CBO). Dutch Guideline for the treatment of severe psoriasis (ultraviolet B, ultraviolet A in combination with oral psoralen, cyclosporin A, methotrexate and acitretine). Alphen aan den Rijn: Van Zuiden Communications B.V. ; 2003.
40. Naldi L, Addis A, Chimenti S, et al. Impact of body mass index and obesity on clinical response to systemic treatment for psoriasis. Evidence from the Psocare project. Dermatology 2008;217(4):365-73.

Chapter 12

Summary/Samenvatting

Summary

In **chapter 1** we provide a general introduction to this thesis. Psoriasis is a chronic skin condition that affects about 2% of the Caucasian population, which can pose a substantial financial burden to society due to its chronic course. The cause of psoriasis is multifactorial, suggesting both a role for genetic and environmental factors that lead to hyperproliferation and abnormal differentiation of epidermal keratinocytes. A range of therapies are available for treating psoriasis varying from topicals, photo(chemo)phototherapy to systemic therapies, although no cure still exists. We end this introduction by discussing why psoriasis is considered as a problem from several different perspectives and by stating the aims of this thesis.

In **chapter 2** an overview is given of the various comorbidities associated with dermatological diseases such as psoriasis, atopic dermatitis, vitiligo and non-melanoma skin cancer. The associations are often complex, multifactorial and incidental and therefore the validity the various associated comorbidities are critically discussed. Secondly, this review also describes the clinical relevance of studying comorbidities. A skin disease can be an early marker of a potential comorbidity, the presence of comorbidities may also influence clinical management and finally knowledge about comorbidities may increase the understanding of a shared pathogenesis of both diseases.

In **chapter** 3 we describe the available literature on the cardiovascular risk profile in patients with psoriasis. Based on the available literature it is hypothesised that the cardiovascular risk profile of patients with psoriasis may be affected by the chronic low-grade inflammation associated with psoriasis, the sum of anti-inflammatory effects and atherogenic side-effects of systemic therapies and unhealthy life style factors. The chronic pro-inflammatory profile in psoriasis has been described to potentially have various adverse effects such as dyslipidemia, endothelial dysfunction, oxidative stress, hypertension, hyperhomocysteinemia and blood platelet adhesion. However, prospective observational studies are still needed to accurately estimate the cardiovascular risk in psoriasis and to determine the possible underlying processes.

In **chapter 4** we investigated the association between psoriasis and cardiovascular disease by comparing the 5-year prevalence of prescriptions for cardiovascular and anti-diabetic drugs in patients with psoriasis (n=9,804) and a matched reference population (n=15,288). Drug exposure data were extracted from the Dutch PHARMO-Record Linkage System database. Patients with psoriasis were identified using an algorithm of hospitalizations and drug dispensing records specific for psoriasis and matched 1:2 to controls for gender, age and time-period. This study demonstrated that the 5-year prevalence of prescriptions for cardiovascular drugs (i.e. anti-hypertensives, anti-coagulant and anti-platelet agents, nitrates, digoxin and lipid-lowering drugs) and anti-diabetics were higher in the psoriasis cohort than in the reference cohort. In a

multiple linear regression model adjusting for the number of unique prescriptions as a proxy for the consumption of healthcare psoriasis was no longer significantly associated with any of these drug classes. This effect of adjusting illustrates the complexity of studies assessing comorbidities in psoriasis and suggests that medical surveillance bias, in addition to HRQOL impairment and depression therapies and lifestyle factors, is an important confounder.

In **chapter 5**, we compare the incidence of hospitalizations for acute ischemic heart disease (IHD) in a cohort of psoriasis patients to a reference cohort matched for age, gender and cohort entry date. Again, we used the same database. A total of 15,820 psoriasis patients and 27,577 reference subjects were included, showing an incidence rate of 611 and 559 IHD per 100,000 person-years, respectively. The age and gender adjusted risk of IHD was subsequently comparable. Psoriasis patients used more antihypertensive, antidiabetic and lipid lowering drugs and were more often hospitalized, but after adjusting for these variables the risk of IHD remained comparable. Subgroup-analyses neither showed a different risk of IHD in the group of psoriasis patients who only used topicals or those who received systemic therapies or inpatient care for their psoriasis. This study suggests that psoriasis is not a clinically relevant risk factor for IHD hospitalizations on the population level.

In **chapter 6** we describe the largest available population based study to investigate the incidence of all major infectious diseases (IDs) requiring hospitalization in psoriasis patients (n=25,742) compared to reference subjects (n=128,710). This study used the data from the PHARMO-RLS database from 1997 until 2008 and investigated the occurrence of first and multiple IDs requiring hospitalization. The likelihood of both first and multiple IDs in psoriasis patients was twice as high as in the reference population. After adjusting for substantial confounders, which were prescriptions for anti-diabetics and COPD/anti-asthmatic drugs, the adjusted HR decreased to 1.6 (95% CI 1.9-2.2). Comparable adjusted ratios were found for multiple IDs. The likelihood of IDs was highest for patients with severe psoriasis, followed by mild psoriasis patients and the reference cohort ($p<.0.001$ log-rank test) and could not be explained by exposure to systemic anti-psoriatic drugs.

In **chapter 7** the possible associations between psoriasis and several comorbidities are critically discussed. It has been hypothesized that the chronic inflammation in psoriasis patients is the biological explanation for the observed associations. However, these associations are much more complex and multifactorial. Among the confounding factors are unhealthy lifestyle factors due to the decreased health related quality of life, the effect of systemic anti-psoriatic therapies and the detection bias due to increased healthcare consumption among psoriasis patients. Other complex items of interpretating observational studies is the deficiency of proving causality and the translation of absolute versus relative risk differences or even clinical

relevance. Taking this into account, caution is warranted before psoriasis patients are screened and treated differently than other patients independent of other risk factors.

In **chapter 8** we evaluate the awareness, knowledge, attitudes and use of the Dutch guidelines for the treatment of moderate to severe plaque psoriasis by a survey among a large sample of dermatologists in the Netherlands. Of the 353 dermatologists in the Netherlands, 161 (46%) completed the questionnaire. The guidelines were well known, appreciated and considered reliable, although there was some disagreement on the user-friendliness and communication facilitating properties. Dermatologists having a good familiarity with the guidelines also had a more positive view towards them and also reported to used them more often. Its use was also higher among dermatologists with a larger population of psoriasis patients. Increasing the familiarity with these guidelines may result in more positive attitudes and increase its frequency of use.

In **chapter 9** the reimbursement criteria for biological therapies for psoriasis in the Netherlands are evaluated using an anonymous postal survey. The reimbursement criteria were the presence of moderate to severe chronic plaque psoriasis in patients unresponsive, intolerant or with contraindications to PUVA, methotrexate and cyclosporine. Three-quarter of responding dermatologists agreed with introducing this reimbursement system but also found it inconvenient. Criteria that the majority would like to see less strict were the obligated use of cyclosporine and the dosage of 22.5 mg methotrexate weekly. The findings of this survey suggested that failure to respond to UVB or PUVA and methotrexate or cyclosporine are preferred as reimbursement criteria. These survey outcomes combined with the known skin cancer promoting interaction between UV and cyclosporine may stimulate a debate about the reimbursement criteria.

In **chapter 10** some commentary is given on how the Italians have a leading role in both a national (Psocare) and international (Psonet) registry that records items related to effectiveness and safety of systemic anti-psoriatic drugs in a postmarketing setting. This registry has multiple advantages. It provides data on the effectiveness of a therapy in a large heterogeneous population in real life and secondly helps to investigate the effect of demographic, lifestyle and disease characteristics on treatment response. Most therapies had a lower postmarketing effectiveness than reached in RCTs. Obesity, which is one of the comorbidities that is associated with psoriasis, was negatively associated with treatment outcomes for cyclosporine, efalizumab and etanercept. These outcomes confirm the importance of proper assessment for comorbidities since these items should be taken into account in RCTs and clinical practice.

In **chapter 11** the findings from studies presented in this thesis are discussed and put in a broader perspective. First, the complexity of investigating and also interpretating the studies on comorbidities in psoriasis including CVD and infections are further discussed. The deficiency

of psoriasis as a potential useful CV risk factor is additionally illustrated by the criteria for evaluating a new CV risk factor. Furthermore, we describe the developments in the treatment of psoriasis patients over the past ten years and how this among other things has been affected by guidelines, reimbursement criteria and research on the impact of psoriasis on the HRQOL and comorbidities. The discussion ends with future perspectives for further research on comorbidities and postmarketing effectiveness and safety studies of systemic therapies.

Samenvatting

In **hoofdstuk 1** geven we met een algemene inleiding tot dit proefschrift. Psoriasis is een chronische huidziekte, waarbij ongeveer 2% van de Kaukasische bevolking is aangedaan. Door het chronische beloop is ook de financiële impact op de maatschappij aanzienlijk. De oorzaak van psoriasis is multifactorieel, bestaande uit een combinatie van zowel genetische als omgevingsfactoren die uiteindelijk leiden tot hyperproliferatie en abnormale differentiatie van epidermale keratinocyten. Een breed repertoire van therapieën is beschikbaar, variërend van locale therapie, foto(chemo)therapie tot systemische therapieën, maar er zijn nog geen curatieve behandelingen. Ten slotte wordt in deze introductie vanuit verschillende standpunten besproken waarom psoriasis een probleem is.

In **hoofdstuk 2** wordt een overzicht gegeven van de verschillende comorbiditeiten die geassocieerd zijn met dermatosen zoals psoriasis, atopische dermatitis, vitiligo, basaalcelcarcinomen en plaveiselcelcarcinomen. De associaties zijn vaak complex, multifactorieel en incidenteel, waardoor een kritische evaluatie van de beschreven associaties of soms zelfs causale relaties noodzakelijk is. Deze review beschrijft ook de klinische relevantie van het bestuderen van comorbiditeiten. Een huidziekte kan bijvoorbeeld een vroege marker zijn van een potentiële comorbiditeit. Daarnaast kunnen comorbiditeiten invloed hebben op het klinische beleid en/of bijdragen een toegenomen kennis van potentiële gedeelde pathogenetische mechanismen van beide ziekten.

In **hoofdstuk 3** beschrijven we de beschikbare literatuur over het cardiovasculaire risicoprofiel van patiënten met psoriasis. Op basis van deze literatuur werd de hypothese geïntroduceerd dat het cardiovasculaire risicoprofiel van patiënten met psoriasis ongunstig wordt beïnvloed door; de chronische laaggradige ontsteking geassocieerd met psoriasis, de optelsom van anti-inflammatoire en pro-atherogene bijwerkingen van systemische therapieën en ongezonde leefstijlfactoren. Het chronische pro-inflammatoire profiel van psoriasis patiënten zou ongunstige cardiovasculair effecten hebben zoals dyslipidemie, endotheeldysfunctie, oxidatieve stress, hypertensie, hyperhomocysteinemie en verhoogde adhesie van thrombocyten. Prospectieve observationele studies zijn echter nodig om een accurate schatting te kunnen maken van het cardiovasculaire risicoprofiel van psoriasis patiënten en van de onderliggende mechanismen.

In **hoofdstuk 4** onderzoeken we de associatie tussen psoriasis en cardiovasculaire ziekten door het vergelijken van de 5-jaars prevalentie van cardiovasculaire en anti-diabetische medicatie in patiënten met psoriasis (n=9,804) en een gematchte referentie populatie (n=15,288). De gegevens over medicatieblootstelling zijn afkomstig uit de Nederlandse PHARMO-Record Linkage System database. Psoriasis patiënten werden geselecteerd door middel van een algoritme van ziekenhuisontslag-diagnoses en prescriptiedata specifiek voor psoriasis en 1:2 gematcht

met controles voor geslacht, leeftijd en tijdsperiode. Deze studie toonde dat de 5 jaars prevalentie van prescripties voor cardiovasculaire medicatie (bv. antihypertensiva, anticoagulantia, plaatjesaggregatieremmers, nitraten, digoxine en lipidenverlagende geneesmiddelen) en antidiabetica hoger was in het psoriasis dan in het referentie cohort. In de multivariate lineaire regressie model waarin aangepast werd voor het unieke aantal prescripties als een proxy voor de mate van gezondheidszorgconsumptie, was psoriasis niet langer significant geassocieerd met deze medicatiegroepen. Dit effect illustreert de complexiteit van studies naar comorbiditeiten bij psoriasis en suggereert dat detectie bias naast de kwaliteit van leven, depressies, therapieën en leefstijlfactoren, een belangrijke confounder is.

In **hoofstuk 5** vergelijken we de incidentie van opnames voor acute ischemische hartziekten (IHZ) in een cohort van psoriasis patiënten met een voor leeftijd, geslacht en start van follow-up gematcht referentie cohort. Hiervoor hebben we wederom de PHARMO database gebruikt. In totaal werden 15,820 psoriasis patiënten en 27,577 referentie personen geïncludeerd met een incidentie van respectievelijk 611 en 559 IHZ per 100,000 persoonsjaren. Het voor leeftijd en geslacht aangepaste risico was ook vergelijkbaar tussen beide cohorten. De psoriasis patiënten gebruikten meer anithypertensiva, antidiabetica en lipidenverlagende medicatie en waren vaker opgenomen geweest, maar na aanpassen voor deze variabelen bleef het risico op IHZ vergelijkbaar tussen beide cohorten. Subgroep analyse liet ook geen ander risico zien op IHZ in de groep psoriasis patiënten die alleen topicale therapieën hadden gebruikt en de groep psoriasis patiënten die een systemische therapie had gebruikt of ter behandeling opgenomen was geweest. De uitkomsten van deze studie suggereren dat op populatieniveau psoriasis geen klinisch relevante risicofactor is voor opname voor IHZ.

In **hoofdstuk 6** beschrijven we de tot nu toe grootste beschikbare populatie gebaseerde cohort studie naar de incidentie van de voornaamste infectieziekten waarvoor ziekenhuisopname noodzakelijk is bij 25,742 psoriasis patiënten en 128,710 controle personen. De PHARMO database met gegevens verzameld tussen 1997 en 2008 werd in deze studie gebruikt voor het bepalen van de incidentie van eerste en multiple infectieziekten waarvoor ziekenhuisopname noodzakelijk was. De kans op zowel een eerste als multipele infectieziekten was bij psoriasis patiënten twee keer zo hoog als in de referentie populatie. Na aanpassen voor substantiële confounders, zoals prescripties voor antidiabetica en COPD/astma medicatie, nam de aangepaste hazard ratio af naar 1.6 (95% CI 1.9-2.2). De aangepaste ratio's waren vergelijkbaar voor multipele infectieziekten. De kans op een infectieziekte was het hoogste voor patiënten met ernstige psoriasis, gevolgd door patiënten met milde psoriasis en tenslotte het referentie cohort ($p<0.001$ log-rank test) en kon niet verklaard worden door blootstelling aan systemische therapieën.

In **hoofdstuk 7** worden de mogelijke associaties tussen psoriasis en de verschillende comorbiditeiten kritisch besproken. De hypothese is dat de chronische inflammatie bij patiënten met psoriasis een mogelijke biologische link vormt voor de gevonden associaties. In werkelijkheid zijn deze associaties veel complexer en multifactorieel. Belangrijke confounders zijn hierbij ongezonde leefstijlfactoren vaak als gevolg van de verminderde kwaliteit van leven, het effect van systemische medicatie voor psoriasis en de detectie bias door de verhoogde gezondheidszorgconsumptie van patiënten met psoriasis. Andere items die de interpretatie van observationele studies bemoeilijken is het aantonen van causaliteit en de interpretatie van absolute versus relatieve risicoverschillen of zelfs klinische relevantie. Hiermee rekening houdend is voorzichtigheid geboden voordat onafhankelijk van andere risicofactoren psoriasis patiënten extra gescreend en anders behandeld worden dan andere patiënten.

In **hoofdstuk 8** evalueren we de bekendheid, kennis, toepassing en meningen over de Nederlandse richtlijnen voor de behandeling van matige tot ernstige plaque psoriasis door middel van een vragenlijst onder de leden van de Nederlandse Vereniging voor Dermatologie en Venereologie. De vragenlijst werd uiteindelijk door 161 (41%) van de 353 benaderde dermatologen ingevuld. De richtlijnen zijn goed bekend en worden gewaardeerd en als betrouwbaar beschouwd. De meningen waren wel verdeeld over de gebruiksvriendelijkheid en communicatie verbeterende aspecten van de richtlijnen. Naarmate dermatologen beter bekend waren met de richtlijnen was hun houding ook positiever ten opzichte van de richtlijnen en rapporteerden ze er ook vaker gebruik van te maken. Het gebruik van de richtlijnen was ook positief geassocieerd met de grootte van de populatie psoriasis patiënten. Verdere verbetering van de bekendheid met de richtlijnen zorgt mogelijk voor een nog betere waardering en toename in gebruik.

In **hoofdstuk 9** worden de vergoedingscriteria van biologicals voor de behandeling van psoriasis in Nederland geëvalueerd door middel van een anonieme schriftelijke vragenlijst. De vergoedingscriteria bestonden uit de aanwezigheid van matige tot ernstige psoriasis vulgaris in de patiënten bij wie er sprake was van ineffectiviteit, contraindicaties en/of intolerantie voor PUVA, methotrexaat en cyclosporine. Driekwart van de reagerende dermatologen was het eens met de introductie van dit vergoedingssyteem maar zij vonden dit tegelijkertijd ook een lastig systeem. Criteria die de meerderheid graag minder streng zou zien was het obligate gebruik van cyclosporine en de verplichte minimale dosering van 22.5 mg methotrexaat per week. De uitkomsten van deze enquête suggereren dat ineffectiviteit van UVB of PUVA en methotrexaat of cyclosporine geprefereerd worden als vergoedingscriteria. Deze resultaten, gecombineerd met de bekende huidkanker inducerende interactie tussen UV en cyclosporine, heeft misschien een stimulerend effect op het debat over de vergoedingscriteria.

In **hoofdstuk 10** geven we onze mening over de leidende rol van de Italianen in zowel de nationale (Psocare) en internationale (Psonet) database waarin data worden geregistreerd die betrekking hebben op de effectiviteit en veiligheid van systemische psoriasis medicatie in een postmarketing setting. Dit register heeft verschillende voordelen. Op deze wijze worden er data verzameld over de werkelijke effectiviteit van een therapie in een grote heterogene populatie en daarnaast helpt het om het effect van demografische, leefstijl en ziekte karakteristieken op de behandeluitkomst te bepalen. Veel therapieën bleken een lagere postmarketing effectiviteit te hebben dan in RCTs. Overgewicht, een van de comorbiditeiten geassocieerd met psoriasis, was een negatieve predictor voor de behandelresultaten van ciclosporine, efalizumab en etanercept. Deze resultaten bevestigen het belang van comorbiditeiten voor zowel RCTs als de dagelijkse praktijk.

In **hoofdstuk 11** worden de resultaten van de gepresenteerde studies in een breder perspectief geplaatst. Allereerst bespreken we de complexiteit van onderzoek naar en de interpretatie van studies over comorbiditeiten bij psoriasis zoals hart- en vaatziekten en infecties. De tekortkoming van psoriasis als een potentiële cardiovasculaire risicofactor wordt verder geïllustreerd aan de hand van de criteria ter evaluatie van een nieuwe cardiovasculaire risicofactor. Vervolgens beschrijven we de ontwikkelingen in de behandeling van psoriasis patiënten over de afgelopen 10 jaar en hoe dit onder andere beïnvloed is door de richtlijnen, vergoedingscriteria en onderzoek naar de impact van psoriasis op de kwaliteit van leven en comorbiditeiten. Ten slotte bespreken we toekomstige perspectieven voor verder onderzoek naar comorbiditeiten en postmarketing effectiviteit en veiligheidsstudies van systemische therapieën.

Chapter 13

Dankwoord

List of co-authors

List of publications

Curriculum Vitae

PhD Portfolio

Dankwoord

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List of co-authors

presented in this thesis

Affiliations at the time at which the research was conducted

Pieter van den Haak
PHARMO, Institute for Drug Outcome Research, Utrecht, The Netherlands.

Ron M.C. Herings
PHARMO, Institute for Drug Outcome Research, Utrecht, The Netherlands.
and
Institute of Health Policy & Management, Erasmus University Medical Centre, Rotterdam, The Netherlands.

Elke M. de Jong
Department of Dermatology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands.

Marjolein Lugtenberg
Department of Tranzo, Tilburg University, Tilburg, The Netherlands.

Willemijn M. Meijer
PHARMO, Institute for Drug Outcome Research, Utrecht, The Netherlands.

Martino H.A.M. Neumann
Department of Dermatology, Erasmus University Medical Centre, Rotterdam, The Netherlands.

Tamar E.C. Nijsten
Department of Dermatology, Erasmus University Medical Centre, Rotterdam, The Netherlands.

Errol P. Prens
Department of Dermatology, Erasmus University Medical Centre, Rotterdam, The Netherlands.

Eric J.G. Sijbrands
Department of Internal Medicine, Erasmus University Medical Centre, Rotterdam, The Netherlands.

Phyllis I. Spuls
Department of Dermatology, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands.

H. Bing Thio
Department of Dermatology, Erasmus University Medical Centre, Rotterdam, The Netherlands.

Gert P. Westert
Department of Tranzo, Tilburg University, Tilburg, The Netherlands.
And
The National Institute of Public Health and the Environment (RIVM), Bilthoven, The Netherlands.

Esther de Vries
Department of Public Health, Erasmus University Medical Centre, Rotterdam, The Netherlands.
And
Department of Dermatology, Erasmus University Medical Centre, Rotterdam, The Netherlands.

List of publications

Wakkee M, Thio HB, Prens EP, Sijbrands EJ, Neumann HA. Unfavorable cardiovascular risk profiles in untreated and treated psoriasis patients.
Atherosclerosis. 2007 Jan;190(1):1-9. Epub 2006 Aug 30. Review.

Wakkee M, Thio HB. BG-12, an immunomodulatory dimethylfumarate.
Curr Opin Investig Drugs. 2007 Nov;8(11):955-62.

Wakkee M, Thio HB, Spuls PI, de Jong EM, Nijsten T. Evaluation of the reimbursement criteria for biological therapies for psoriasis in the Netherlands. Br J Dermatol. 2008 May;158(5):1159-61.

Wakkee M, Assen YJ, Thio HB, Neumann HAM. Repigmentation of vitiligo during efalizumab treatment. Journal of the American Academy of Dermatology. 2008 Aug. 59 (2 Suppl 1):S57-8.

Wakkee M, Lugtenberg M, Spuls PI, de Jong EM, Thio HB, Westert GP, Nijsten T. Knowledge, attitudes and use of the guidelines for the treatment of moderate to severe plaque psoriasis among Dutch dermatologists. Br J Dermatol. 2008 Aug;159(2):426-32.

Nijsten T, Wakkee M. Psocare: Italy shows the way in postmarketing studies. Dermatology. 2008;217(4):362-4.

Wakkee M, Nijsten T. Comorbidities in dermatology. Dermatol Clin 2009;27:137-47.

Nijsten T., Wakkee M. Complexity of the association between psoriasis and comorbidities. J Invest Dermatol. 2009;129:1601-3.

Wakkee M, Meijer W, Neumann HAM, Herings RMC, Nijsten T. Psoriasis may not be an independent predictor for the use of cardiovascular and antidiabetic drugs: a 5-year prevalence study. Acta Derm Venereol. 2009;89(5):476-83.

Wakkee M, Herings RMC, Nijsten T. Psoriasis may not be an independent risk factor of acute ischemic heart disease hospitalizations: results of a large population based Dutch cohort. J Invest Dermatol. 2009 Oct 8. [Epub ahead of print]

Wakkee M, Nijsten T. De medicamenteuze behandeling van psoriasis (The medical treatment of psoriasis). Farmacotherapie Online. 2009. http://www.farmacotherapie.org/home

Wakkee M, Nijsten T. Psoriasis en obesitas, meer dan een toevallige Combinatie (Psoriasis and obesity, more than an accidental combination). Modern Medicine. Jan 2010:42-4.

Curriculum Vitae

Marlies Wakkee werd op 12 maart 1981 geboren te Dordrecht. In 1999 behaalde zij haar V.W.O. diploma aan het Thuredrecht College te Dordrecht. Nadat zij was uitgeloot voor de studie geneeskunde, koos zij voor de Hogere Europese Beroepen Opleiding in Den Haag, waar zij na het behalen van haar propedeuse in 2000 alsnog mocht starten met de studie Geneeskunde aan de Erasmus Universiteit te Rotterdam. Na haar reguliere coschappen in het St. Elisabeth Ziekenhuis te Tilburg, verrichte zij haar oudste co-schap en afstudeeronderzoek naar "het ongunstige risicoprofiel van patiënten met psoriasis" onder supervisie van dr. H.B. Thio op de afdeling Dermatologie in het Erasmus MC. Het doctoraalexamen werd behaald in maart 2006 en het artsexamen in juli 2006. Aansluitend werkte zij als arts-assistent op de afdeling Dermatologie in het Erasmus MC, waarbij zij onderzoek combineerde met uitvoeren van verschillende klinische trials voornamelijk op het gebied van biologicals bij psoriasis patiënten. In januari 2007 begon zij onder supervisie van Dr. T. Nijsten aan het huidige proefschrift en in juli 2008 werd zij aangenomen voor de opleiding Dermatologie in Rotterdam. Zij trouwde op 22 juni 2007 met Adem Özgur en sinds 28 augustus 2008 zijn zij de trotse ouders van Atilla.

PhD Portfolio

Summary of PhD training and teaching activities

Name PhD student: Marlies Wakkee

PhD period: January 2007 – December 2009

Erasmus MC Department: Dermatology

Promotor: Prof.Dr. H.A.M. Neumann

Supervisor: Dr. T. Nijsten and Dr. R.M.C. Herings

	Year	Workload (Hours/ ECTS)
1. PhD training		
General academic skills		
Biomedical English Writing and Communication	2009	4 ECTS
Research skills		
- NIHES course: Pharmaco-epidemiology	2007	0.7 ECTS
- NIHES course: Clinical Trials	2007	0.7 ECTS
- NIHES course: Regression analysis	2007	1.4 ECTS
- NIHES course: Introduction to Data-analysis	2007	0.7 ECTS
- NIHES course: Principles of Research in Medicine and Epidemiology	2007	0.7 ECTS
- NIHES course: Survival Analysis for Clinicians	2008	1.4 ECTS
- NIHES course: Conceptual Foundation of Epidemiologic Study Design	2008	0.7 ECTS
- Evidence based Medicine Course, Erasmus MC, Rotterdam, The Netherlands	2009	8 hours

	Year	Workload (Hours/ ECTS)
Presentations		
- **Wakkee M**, Thio HB, Sijbrands EJG, Neumann HAM. "Unfavorable cardiovascular risk profiles in untreated and treated psoriasis patients." Presented (poster) at the European Workshop on Immune-Mediated Inflammatory Diseases, Amsterdam, the Netherlands (28 September)	2006	1 ECTS
- **Wakkee M**, Nijsten T. "Comorbidities with psoriasis." Presented at Dermatology Immunology Symposium. Amsterdam, the Netherlands (5 April).	2008	1 ECTS
- **Wakkee M**, Thio HB, Neumann HAM. "Efalizumab: effectief bij vitiligo?" Presented at Stichting Nederlandstalige Nascholing voor Dermatologie en Venereologie, Antwerp, Belgium (19 April).	2008	1 ECTS
- **Wakkee M**, Nijsten T. "Is psoriasis an independent risk factor for using cardiovascular and antidiabetic drugs?" Presented at Eilanddagen 2008, Schiermonnikoog, the Netherlands (23 June).	2008	1 ECTS
- **Wakkee, M**; van der Linden, M; Nijsten, T. J "Psoriasis appears not to be directly related with using cardiovascular and antidiabetic drugs." Presented at IDEA congress 2008, United Kingdom, Nothingham (9 September).	2008	1 ECTS
- **Wakkee M**, Herings RMC, Nijsten T. "Psoriasis is not associated with an increased risk of cardiovascular hospitalizations: results of a large population based cohort." Presented at ESDR Budapest, Hungary (10 September).	2009	1 ECTS
- **Wakkee M**. "Staat een huidziekte alleen?" Presented at Huidfondsmiddag, Rotterdam, the Netherlands (18 November)	2009	1 ECTS
- **Wakkee M,** Nijsten T. "Het risico op ernstige infecties bij patiënten met psoriasis: resultaten van een grote populatie gebaseerde cohort studie." Presented at the 11de wetenschappelijke jaarvergadering van de Nederlandse Vereniging voor Experimentele Dermatologie, Lunteren, the Netherlands (5 February)	2010	1 ECTS

	Year	Workload (Hours/ ECTS)
International conferences		
- European Workshop on Immune-Mediated Inflammatory Diseases , Amsterdam, Netherlands (27-29 September).	2006	1 ECTS
- Congress of the European Academy of Dermatology and Venereology, Rhodes, Greece (4-8 October).	2006	1 ECTS
- 69th Annual Meeting of the SID, Montreal, Canada (6-9 May).	2009	1 ECTS
- 39th Annual ESDR Meeting, Budapest, Hungary (9-12 September)	2009	1 ECTS
Seminars and workshops		
- Systemic therapy and psoriasis, interactive workshop, Rotterdam, the Netherlands (7 june).	2006	1 ECTS
- There's no excuse for writing unreadable scientific articles! by David Alexander.	2008	1 hour
- Time Management.	2008	1 hour
- PhD day, Erasmus MC.	2008	6 hours
- Success in research: Learn from the experts.	2009	1 hour
- Publishing and Acceptance Criteria for Scientific Journals, by Ian Cressie.	2009	2 hours
- Workshop on drug exposure ascertainment - Division Pharmacoepidemiology & Pharmacotherapy.	2009	2.5 hours
- Symposium patients, people and populations. 40 years of epidemiology at Erasmus.	2009	5.5 hours
- CPO autumn symposium 2009, Cost-Effective Interventions in Health Care: From Evaluation to Application.	2009	2.5 hours

	Year	Workload (Hours/ ECTS)
Other		
- Dermatology Immunology Symposium: NMSC and psoriasis. Amsterdam, the Netherlands.	2008	1 ECTS
- Stichting Nederlandstalige Nascholing voor Dermatologie en Venereologie – Therapeutical innovations.	2008	1 ECTS
- Eilanddagen 2008. Schiermonnikoog, the Netherlands.	2008	1 ECTS
- Book club: Clinical Prediction Models, Steyerberg E.W.	2009	2 hours
Occasional reviewer for:		
- Journal of Experimental Dermatology	2007 – present	4 hours
- Archives of Dermatological Research	2008 – present	4 hours
- Acta Dermato-Venereologica	2008 – present	8 hours
- Journal of the European Academy of Dermatology	2008 – present	12 hours
- Journal of Investigative Dermatology	2008 – present	16 hours
- Dermatology	2008 – present	4 hours

2. Teaching activities

Assisting/supervising junior researchers:	
- C. Holterhues, MD-PhD student Dermatology, Erasmus MC Rotterdam. Thesis on melanoma.	2009
- S.W.I. Reeder, PhD student and resident Dermatology, Erasmus MC Rotterdam. Thesis on ulcus cruris venosum, measurement of venous pressure, varicose veins.	2009
Organisation and programme coordinator of weekly residents' education. Department of dermatology, Erasmus MC Rotterdam	2009-present