

German S3-guidelines on the treatment of psoriasis vulgaris (short version)

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Abstract Psoriasis vulgaris is a common and often chronic inflammatory skin disease. The incidence of psoriasis in Western industrialized countries ranges from 1.5 to 2%. Patients afflicted with severe psoriasis vulgaris may experience a significant reduction in quality of life. Despite the large variety of treatment options available, patient surveys have revealed insufficient satisfaction with the efficacy of available treatments and a high rate of medication non-compliance (Richards et al. in *J Am Acad*

Dermatol 41(4):581–583, 1999). To optimize the treatment of psoriasis in Germany, the Deutsche Dermatologische Gesellschaft (DDG) and the Berufsverband Deutscher Dermatologen (BVDD) have initiated a project to develop evidence-based guidelines for the management of psoriasis first published in 2006 and now updated in 2011. The Guidelines focus on induction therapy in cases of mild, moderate, and severe plaque-type psoriasis in adults. This short version of the guidelines presents the resulting series

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of therapeutic recommendations, which were based on a systematic literature search and discussed and approved by a team of dermatology experts. In addition to the therapeutic recommendations provided in this short version, the full version of the guidelines includes information on contraindications, adverse events, drug interactions, practicality, and costs, as well as detailed information on how best to apply the treatments described (for full version please see Nast et al. in JDDG Suppl 2:S1–S104, 2011 or <http://www.psoriasis-leitlinie.de>).

Keywords Evidence-based guidelines · Psoriasis vulgaris · Treatment

Introduction

The Deutsche Dermatologische Gesellschaft and the Berufsverband Deutscher Dermatologen have initiated a project to develop evidence-based guidelines for the treatment of plaque psoriasis which were published in 2006 and now updated in 2011 [152, 155]. The full version has again been published in the Journal der Deutschen Dermatologischen Gesellschaft (JDDG 2011 Supplement 2 [152]) and is available at <http://www.psoriasis-leitlinie.de>. This article summarizes the key messages from the guidelines.

Background

Needs analysis/challenges in patient care

Psoriasis vulgaris is a common and almost always chronic skin disease

The prevalence of psoriasis in Western industrialized nations is 1.5–2% [157]. About 80% of psoriasis patients have the plaque form of disease. In Germany, the disease affects an estimated 1.6 million people. More than 90% have chronic disease [157].

Patients with plaque psoriasis have a substantially impaired quality of life

Studies on the impairment of quality of life in psoriasis patients have shown that, depending on the severity of disease, related disability or psychosocial stigmatization can present a considerable burden for the patient [198]. Patient surveys have found that the impact on quality of life is comparable to that experienced by patients with type 2 diabetes or chronic lung disease [183].

Patient satisfaction with current therapies is low and compliance is poor

Based on the results of patient surveys, only about one-fourth of patients report being very satisfied with the results of therapy; about 50% are moderately satisfied, and about one-fifth are not very satisfied [206]. There is also a high rate of medication non-compliance (up to 40%) [188]. Reasons for non-compliance include poor tolerability, fear, lacking information about potential side effects, low efficacy, and complicated usage [187, 242].

There is uncertainty concerning the use of systemic therapies

Nast et al. reported in a small survey of 39 dermatologists in private practice that, according to their own self-assessment, 76% of doctors surveyed had some uncertainty about prescribing systemic medications. 79% said they believed that this led to inadequate treatment with systemic therapies [153].

There is inadequate use of systemic therapy options in patients with moderate-to-severe psoriasis

Nast et al. reported in a study from 2006 with 54 dermatologists in private practice that in visits with 2,294 patients with moderate-to-severe psoriasis, about 50% of patients were treated with topical therapies alone. 17% received additional UV therapy and only about 30% were taking some form of systemic therapy [156].

The economic costs of disease are high

The costs of psoriasis, including the costs of statutory health care and other forms of insurance (e.g., unemployment coverage) as well as the costs for the patient himself (e.g., for basic therapies), are about 2,866 € per patient per year [19]. In 2002, about 20,000 patients with psoriasis vulgaris were hospitalized, primarily for initial treatment as well as for severe flare-ups. One German statutory health insurer (AOK West) reported that the number of disability cases for psoriasis vulgaris per year was 7.35 for men and 4.94 for women/10,000 insured persons (28 and 27 days) [216].

Goal of the guidelines

The overall goal of the guidelines is to provide dermatologists in private practice and clinicians with an accepted, evidence-based tool that can aid decision-making in the selection and implementation of appropriate and adequate therapies for patients with psoriasis vulgaris. The focus of

the guidelines is on induction therapy for mild to severe psoriasis vulgaris in adult men and women.

Improved patient care through implementation of guideline recommendations and optimization of physician knowledge of reported treatment efficacies

The personal experience of physicians and the use of traditional treatment concepts for psoriasis vulgaris should be augmented or even replaced by an evidence-based assessment of the anticipated results of a given therapy option based on medical science.

Assistance with optimal treatment implementation

The detailed description of systemic therapies, phototherapies, and photochemotherapy, including precise descriptions of their use and safety aspects, should help reduce any reservations on the part of doctors and patients with regard to certain therapies and ensure prompt, sufficient, and optimal treatment. The timely provision of information and prompt induction of adequate therapy should help prevent severe disease which frequently involves hospitalization and lost work days.

Improved patient awareness of current therapy options

A further version of the guidelines, designed for use by the patient, is currently being developed. The aim is to give patients an overview of possible therapies in terms of complications and optimal usage.

Enhancing compliance

Adequate patient compliance/adherence are often related to a good ratio between the benefits of therapy and the related effort, costs, and potential side effects. The choice of an effective therapy by the patient and doctor, taking into account the quality of life variables measured in recent studies, should help ensure a high treatment benefit. Providing information on the prevention and management of adverse effects should help limit or even prevent them. This in turn also increases compliance.

Quality of care indicators

Radtke et al. [180] have proposed eight indicators based on the Delphi method for measuring the quality of care of psoriasis patients. These quality indicators may be applied to the total population of psoriasis patients or used as indicators for monitoring changes in quality of care as a result of the guidelines: (1) average PASI in the total population; (2) average DLQI in the total population; (3)

proportion of patients out of the total population with severe psoriasis vulgaris as measured by PASI (>20); (4) proportion of patients out of the total population who have severe psoriasis vulgaris as measured by DLQI (>10); (5) proportion of patients out of the total population who have previously received systemic therapy; (6) proportion of patients with severe psoriasis (PASI > 20) who report prior or current systemic therapy; (7) proportion of patients out of the total population who have been hospitalized in the last 5 years due to psoriasis; (8) average number of lost work days due to psoriasis among the total population.

Methods

A detailed description of the methods and procedures used for developing the guidelines may be found in the methods report (<http://www.psoriasis-leitlinie.de>). These guidelines are an update of the guidelines published in 2006 [154, 155].

Basis of data

A systematic literature search of published articles up to November 2009 was performed to evaluate the efficacy of various individual therapies. In addition to the 6,224 publications yielded by the literature search in the first version of the guidelines, we identified 1,443 new studies. Of these, 155 studies fulfilled the criteria for inclusion in the current guidelines and were included in the evaluations of treatment efficacy. The methodological quality of the chosen studies was determined using a “literature evaluation form” (LEF). Other aspects included in the guidelines were evaluated on the basis of information from the literature (without a systematic assessment) as well as on the basis of the personal experience of the guidelines expert committee. For 2006/2007, the results of the literature search for the EU guidelines were also included.

Evidence assessment

The efficacy of each intervention was systematically assessed using evidence-based criteria.

The methodological quality of each study was assessed using grades of evidence:

- A₁ Meta-analysis containing at least one randomized grade A₂ study. The results of the various studies included must be consistent.
- A₂ Randomized, double-blind, high-quality clinical comparative study (e.g., sample size calculation, flow chart, ITT analysis, sufficient sample size).
- B Randomized clinical study of lesser quality or other comparative study (non-randomized: cohort study or case–control study).

C Non-comparative study.

Evidence levels were also determined as part of evaluating the effectiveness of a drug given as monotherapy. This consisted of an evaluation of the overall evidence on the intervention:

1. Intervention is supported by grade A₁ studies or mostly consistent results from grade A₂ studies.
2. Intervention is supported by grade A₂ studies or grade B studies with mostly consistent results.
3. Intervention is supported by grade B studies or grade C studies with mostly consistent results.
4. Little or no systematic empirical evidence.

Passages requiring consensus

The authors of the guidelines have defined certain particularly relevant sections as requiring consensus. These passages were agreed on in consensus conferences and are highlighted in gray boxes.

Treatment recommendations

At present there is no clear step-by-step procedure or strict clinical algorithm for the treatment of psoriasis vulgaris. The criteria for selecting an appropriate therapy are complex. Certain aspects related to selecting a suitable treatment must be assessed and weighed individually. The decision for or against a therapy is made on an individual basis. The guidelines provide a scientifically based aid for decision-making and selection of an appropriate treatment. As such they constitute a medical tool for the optimal use of a necessary therapy.

Key recommendations formulated in the text are augmented by symbols representing the strength of the treatment recommendation. The following symbols have been used to help standardize the treatment recommendations:

↑↑	Measure is recommended	(strongly recommended)
↑	Measure may be recommended	(recommended)
→	Measure may be considered	(neutral recommendation)
↓	Measure cannot be recommended	(recommendation against its use)
↓↓	Measure should be avoided	(strongly disadvised)

Due to the focus of the guidelines on induction therapy, the recommendations in the update are limited to this phase. Some recommendations from the previous version are thus no longer included. This is in the interest of standardization and does not indicate any change to the recommendation level of a previously described drug.

The strength of recommendation takes into account various aspects concerning its effectiveness, including evidence level, safety aspects, feasibility, cost-to-benefit

ratio, etc. The strength of the recommendations was agreed on in the framework of a consensus conference.

Results

Therapeutic strategies (Fig. 1)

Evaluation of topical and systemic therapies in tabular form

The following tables are intended to serve as a rough guide for evaluating therapy options. Cumulative calculations of individual aspects in the overall evaluation are not possible and cannot be used for a conclusive evaluation of a given therapy option. Each column should be viewed separately. The evaluation may vary significantly on a case-by-case basis. The varying degrees of severity of psoriasis render a direct comparison between systemic and topical therapies impossible. The evaluations are based on a literature review and expert opinion.

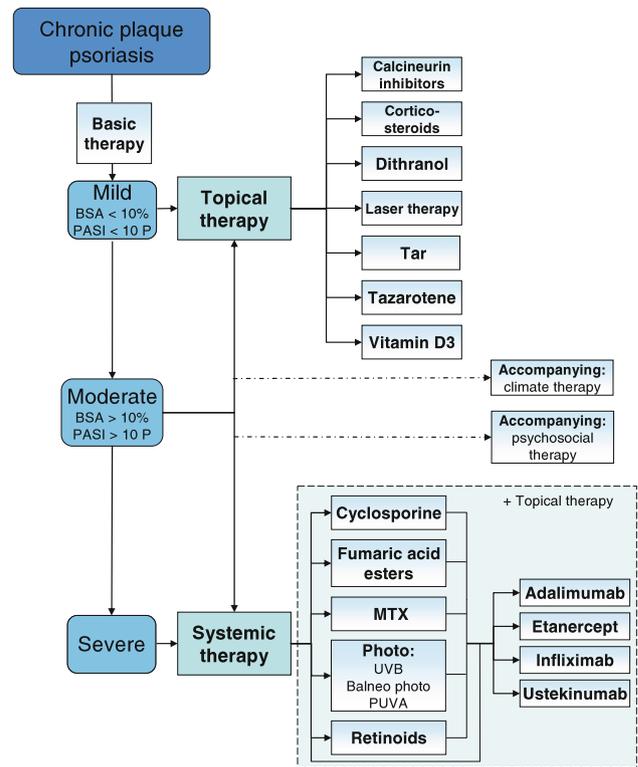


Fig. 1 Overview of therapy options under evaluation for use in chronic plaque psoriasis (the order of therapies is alphabetical and does not represent a ranking)

Topical monotherapy

Therapy	Efficacy	Evidence level	Safety/tolerability of induction therapy	Safety/tolerability for maintenance therapy	Feasibility (patient)	Feasibility (doctor)	Cost/benefit
Calcineurin inhibitors	++	2/3	++	Not indicated	++	– ^a	++
Dithranol	+++	2	++	Not indicated	+ ^b – ^c	+ ^b – ^c	+++
Corticosteroids	++++ ^d	1	+++	+	++	+++	+++
Coal tar	±	4	+	Not indicated	–	±	–
Tazarotene	++	2	++	++	± ^e	± ^e	++
Vitamin D3 derivatives	+++	1	+++	+++	+++	+++	++

Global assessment:



^a No strong consensus (>75%) was achieved using the DELPHI method. The recommendation was therefore made based on a majority vote of 54% (guideline expert committee). Alternatively, members voted for “++.” The reason for the discussion was “off-label” prescribing. The opinions on the effort involved diverged significantly

^b Inpatient

^c Outpatient

^d At least class III steroids; also applies to fixed dose drug combinations

^e No strong consensus (>75%) was achieved using the DELPHI method. The recommendation was therefore made based on a majority vote of 69% (guideline expert committee). Alternatively, members voted for “–.” The reason for the discussion was the poor availability, i.e., available only via international pharmacies. The opinions on the effort involved diverged significantly

Phototherapy and systemic monotherapy

Therapy	Efficacy	Evidence Level	Safety/tolerability of induction therapy	Safety/tolerability of maintenance therapy	Feasibility (patient)	Feasibility (doctor)	Cost/benefit ^g
Phototherapy							
UVB	+++	2	+++	Not indicated	±	+	++
PUVA	+++ to +++++	2	+ ^a ++ ^b	Not indicated	–	±	++
Adalimumab	+++	1	++	++	+++	++	+
Etanercept	+ ^d + ^e ++ ^f	1	++	++	+++	++	±
Cyclosporine	++ to +++	1	+	+	+++	++	++
Fumarate	++	2	+	+++	++	+++	+++
Infliximab	+++ to +++++	1	+	++	+++	±	+
Methotrexate	+ to ++	2	+	++	++	++	+++
Retinoids ^c (systemic)	+	2	+	+	+	++	±
Ustekinumab	+++	1	++	++	+++	++	+

Global assessment:



^a Systemic PUVA

^b Bath/cream PUVA

^c Retinoid therapy is generally not advised for women of childbearing age

^d For 1 × 25 mg

^e For 1 × 50 mg

^f For 2 × 50 mg

^g For a 12-week regimen of induction therapy

(a) *Efficacy* The value in the column “efficacy” reflects the percentage of patients who achieved a reduction in PASI score >75%.

Scale	Systemic therapy (%)	Topical therapy (%)
++++	ca. 90	ca. 60
+++	ca. 70	ca. 45
++	ca. 50	ca. 30
+	ca. 30	ca. 15
±	ca. 10	ca. 5
–	not defined	not defined

The evidence level applies to demonstrated efficacy.

(b) *Safety/tolerability of induction/maintenance therapy* The risk of severe side effects or the likelihood of side effects resulting in discontinuation of therapy.

(c) *Feasibility (patient)* Evaluated factors include the amount of time involved in using the therapy, its actual usage, and ease of administration.

(d) *Feasibility (doctor)* Factors that are evaluated include the amount of work involved (documentation, educating the patient, monitoring), requirements for equipment and personnel, time involved for doctor/patient interactions, reimbursement of treatment measures, invoicing problems/risk of recourse claims by insurers.

(e) *Cost/benefit* This is assessed according to the costs of induction or maintenance therapy.

The assessment of safety/tolerability for induction or maintenance therapy, as well as the feasibility of therapy for the doctor and patient, and costs/benefits are measured on a scale of – (poor) to ++++ (good). Grades are based on information from a literature review and expert opinion. No evidence level is cited since it was not specifically included in the literature search.

Evaluation of topical therapies

Calcineurin inhibitors

Table 1 Summary table

Calcineurin inhibitors	
Approval in Germany	
Pimecrolimus	2002 (atopic dermatitis, not approved for use in psoriasis vulgaris)
Tacrolimus	2002 (atopic dermatitis, not approved for use in psoriasis vulgaris)
Recommended initial dosage	Protopic® for use on the face: begin with 0.03% ointment, later increase dosage to 0.1% ointment Elidel® cream: 1–2 ×/daily

Table 1 continued

Calcineurin inhibitors	
Recommended maintenance dosage	Individual treatment modification
Onset of clinical effect	After about 2 weeks
Response rate	40–50% of patients have significant improvement or complete clearance after 6–12 weeks (evidence level: 2)
Main contraindications	Contraindicated in pregnant or nursing women due to lack of data
Important UAEs	Burning of the skin, increased rate of skin infections
Important drug interactions	No known drug interactions
Misc.	Important note: do not combine with phototherapy

Summary evaluation

Out of eight studies on topical calcineurin inhibitors (pimecrolimus, tacrolimus), four met the inclusion criteria of the guidelines. [131,35,163,140] These studies reported a significant improvement or complete clearance of lesions in 40 - 50 % of patients after six to twelve weeks (EL 2).

Topical calcineurin inhibitors may be used in psoriasis patients for the treatment of areas that are sensitive to steroids, especially the face, flexures, and anogenital region.

Undesirable adverse effects such as burning and irritation can occur. The feasibility for the patient is good, but it is limited for the physician due to off-label use of the drug.

Since calcineurin inhibitors are not approved for the treatment of psoriasis vulgaris, off-label-use is the only available option at this time.

Treatment recommendation

Topical application of tacrolimus or pimecrolimus 1 - 2 x/daily may be considered for the treatment of psoriasis vulgaris involving certain areas such as the face, intertriginous regions, and anogenital region. →

Their use on other areas of the body is not advised, given other alternatives, as the data are insufficient and there is lacking approval for their use in psoriasis. ↓

Coal tar

Table 2 Summary table

Coal tar	
Approval in Germany	Listed since 2000 [German Drug Codex (DAC) code: S-170], historical use, various tar-based topical therapies are approved, tar used as an anti-psoriasis drug after 1925 following publication by Goeckermann
Recommended control parameters	Long-term use/large areas of the skin: possible clinical controls of potential development of carcinoma of the skin
Recommended initial dosage	5–20% ointment or gels for local therapy, 1 ×/daily for a few hours
Recommended maintenance dosage	Not suitable for long-term use (max. 4 weeks, DAC 2000)

Table 2 continued

Coal tar	
Onset of clinical effect	After 4–8 weeks, combination use with UV therapy increases effectiveness
Response rate	Insufficient data for assessing response rate to monotherapy (EL 4)
Main contraindications	Pregnancy and nursing
Important UAEs	Color, odor, carcinogenic risk, phototoxicity which is part of the desirable effect
Important drug interactions	No known interactions with external use
Misc.	DAC 2000 (DAC code: S-170), hazardous materials appendix 4, no. 13

Summary evaluation

Of the 21 studies that were evaluated, six met the criteria for inclusion in the guidelines. [16,52,130,69,13,8]
 Given that there is only one monotherapy (grade C) study available, it is impossible to make any conclusive statements on the efficacy of coal tar monotherapy (EL 4). Clinical studies on coal tar with phototherapy have reported mixed results. Studies report that after 15 - 20 treatments with UV therapy, 45 - 80 % of patients achieve at least PASI 75. The additive effect of coal tar, compared with UV therapy alone, has not been sufficiently proven, however.
 The acceptance of coal tar preparations is low due to their color and odor. Given the availability of more effective, lower-risk, and more practical treatment alternatives, the use of coal tar monotherapy for the treatment of plaque psoriasis is largely outdated.
 Only after careful consideration of the therapeutic benefit, and after considering lower-risk therapy alternatives, may coal tar perhaps be used in combination with UVB for the treatment of refractory plaque psoriasis.

Treatment recommendation

Coal tar monotherapy is not recommended for the treatment of psoriasis vulgaris. ↓↓

Under exceptional circumstances, the use of a coal tar preparation in combination with UV therapy may be considered in individual patients for the treatment of psoriasis. →

Table 3 continued

Steroids	
Important UAEs	Folliculitis, perioral dermatitis, skin atrophy
Important drug interactions	None
Misc.	–

Summary evaluation

Out of 122 studies, 36 met the criteria for inclusion in the guidelines. [205,79,50,122,100,20,42,173,202,208,236,60,164,124,134,103,113,12,95,142,229,123,53,194,112,237,144,192,104,166,37,99,58,30,209,210]
 Significant improvement or complete clearance was found in 25 - 77.8 % of patients who used betamethasone dipropionate (EL 1).
 Among patients who were given mometasone there was > 75 % improvement in lesions in 36.3 - 64 % (EL 1)
 Most studies on class IV steroids (clobetasol 17-propionate 2 x/daily) reported PASI 75 in 68 - 89 % of patients (EL 1).
 The effectiveness of topical steroids may be enhanced by additive use of salicylic acid (EL 1).
 The combination with other systemic or topical therapies also leads to improved remission rates. Common combinations include topical vitamin D₃ derivatives.
 No serious adverse effects have been reported during induction therapy. Long-term use steroids can cause various typical side effects such as skin atrophy and telangiectasias.
 Feasibility is good for the patient and doctor.

Treatment recommendation

Induction therapy with class III topical steroids is recommended for patients with mild to moderate psoriasis vulgaris. ↑↑

Induction therapy with class IV topical steroids may be recommended for patients with mild to moderate psoriasis vulgaris after carefully considering the increased efficacy and theoretically increased risk of adverse effects. ↑

Corticosteroids**Table 3** Summary table

Steroids	
Approval in Germany	1956 (psoriasis vulgaris)
Recommended control parameters	None
Recommended initial dosage	1–2 x/daily
Recommended maintenance dosage	Taper after drug takes effect
Onset of clinical effect	After 1–2 weeks
Response rate	For, e.g., beta methasone dipropionate 2 x/daily marked improvement or complete clearance in 46–56% of patients after 4 weeks (EL 1)
Main contraindications	Bacterial, viral skin diseases

Dithranol**Table 4** Summary table

Dithranol	
Approval in Germany	
Psoralon [®]	1983 (psoriasis vulgaris)
Psoradexan [®]	1994 (psoriasis vulgaris)
Micanol [®]	1997 (psoriasis vulgaris)
Recommended control parameters	Intensity of skin irritation
Recommended initial dosage	Start with 0.5% preparation for long-term therapy or 1% for short-contact therapy, increase if tolerated
Recommended maintenance dosage	Not recommended for long-term therapy
Onset of clinical effect	After 2–3 weeks
Response rate	Significant improvement or complete clearance in 30–70% of patients (EL 2)
Main contraindications	Acute, erythrodermic psoriasis, pustular psoriasis
Important UAEs	Burning and redness of the skin in >10%
Important drug interactions	–
Misc.	–

Summary evaluation

Out of 67 evaluated studies, 11 studies on dithranol monotherapy met the criteria for inclusion in the guidelines. [148,4,49,98,136,178,179,209,214,225,3]
 The results of these studies show total remission (PASI reduction of 100 %) in 30 to 70 % and partial remission (PASI reduction of 75 %) in 26 to 100 % of patients after five to eight weeks (EL 2). Drug efficacy may be increased by combining it with calcipotriol-based creams or UVB phototherapy.
 Therapy should be conducted for four to eight weeks. Maintenance or long-term therapies are not feasible with dithranol and do not offer any benefit.
 The safety of the drug is very good. Burning, redness and transitory brown discoloration are the only adverse effects reported. There are no reports of adverse systemic effects.
 Feasibility is limited for outpatient use. Its use is feasible in hospitalized patients, and there is a good cost-to-benefit ratio.
 For the treatment of severe psoriasis vulgaris, combination use with phototherapy or other topical preparations (calcipotriol) may enhance the treatment response and is thus recommended.

Treatment recommendation

Dithranol monotherapy may be recommended for induction therapy in hospitalized patients with mild to moderate plaque psoriasis. ↑

Monotherapy may be considered for outpatient induction therapy in patients with mild or moderate plaque psoriasis. →

Tazarotene

Table 5 Summary table

Tazarotene	
Approval in Germany	1997 (psoriasis vulgaris)
Recommended control parameters	Check for development of skin irritation
Recommended initial dose	Start with 1 ×/daily (evenings) tazarotene gel 0.1% for ca. 1–2 weeks
Recommended maintenance dose	Tazarotene gel 0.1% 1 ×/daily
Onset of clinical effect	After 1–2 weeks
Response rate	After 12 weeks of tazarotene gel 0.1% roughly half of patients show at least 50% improvement (EL 2)
Main contraindications	Pregnant and nursing women
Important UAEs	Pruritus, burning, erythema, irritation
Important drug interactions	Avoid simultaneous use of preparations with irritative and strong drying effects
Misc.	Tazarotene is approved for use in Germany, but is no longer sold and is currently available only as a 0.1% formulation through international pharmacies

Summary evaluation

Seven of the 12 studies evaluated met the criteria for inclusion in the guidelines. [235,74,115,121,81,177,232]
 After about 12 weeks of treatment with tazarotene 0.1 % 1 ×/daily about 50 % of patients achieve at least a 50 % improvement in skin lesions (EL 2).
 Combination therapy with topical steroids can help optimize treatment success and reduce commonly reported skin irritation (EL 2).
 There are no reports of serious side effects related to the drug. Contact with healthy skin should be avoided to prevent irritation.
 Tazarotene is approved for use in Germany, but is no longer on the market. The drug may be ordered through an international pharmacy. This limits the feasibility of its use.

Treatment recommendation

Topical use of tazarotene may be considered in the treatment of mild to moderate psoriasis vulgaris. →

Vitamin D3 and vitamin D3 analogues

Table 6 Summary table

Vitamin D ₃ and analogues	
Approval in Germany	
Calcipotriol	1992 (psoriasis vulgaris)
Tacalcitol	1994 (psoriasis vulgaris)
Calcitriol	1999 (psoriasis vulgaris)
Calcipotriol/ betamethasone	2002 (psoriasis vulgaris)
Recommended control parameters	Check for development of skin irritation
Recommended initial dosage	Calcipotriol: 1–2 ×/daily on affected areas of the skin, maximum 30% of BSA Tacalcitol: 1 ×/daily on affected areas of the skin, maximum 20% of BSA Calcitriol: 2 ×/daily on affected areas of the skin, maximum 35% of BSA
Recommended maintenance dosage	Calcipotriol: 1–2 ×/daily, up to 100 g/ weekly up to 1 year Tacalcitol: 1 ×/daily for 8 weeks to 18 months maximum 15% of BSA with up to 3.5 g/daily Calcitriol: lacking experience with use for longer than 6 weeks
Onset of clinical effect	After 1–2 weeks
Response rate	30–50% patients experience significant improvement or complete clearance after 4–6 weeks (EL 1)
Main contraindications	Disorders with altered calcium metabolism, severe liver and kidney disease
Important UAEs	Skin irritation (redness, itching, burning)
Important drug interactions	Drugs that elevate calcium levels (e.g., thiazide diuretics), avoid concomitant use of topical salicylic acid (inactivation)
Misc.	–

Summary evaluation

Out of 68 evaluated studies, 27 met the criteria for inclusion in the guidelines. [116,243,84,118,123,112,37,194,144,30,53,104,192,162,166,237,85,98,223,225,131,163,58,22,181,1,2]
 The majority of data are on calcipotriol. For treatment of mild to moderate psoriasis, 30 - 50 % of patients treated with calcipotriol achieve significant improvement or complete clearance within a few weeks (EL 1).
 The efficacy of calcitriol and calcipotriol appears comparable based on available studies (EL 1).
 The efficacy and tolerability of vitamin D₃ derivatives can be further enhanced by combining them with topical steroids (EL 1).
 There are only a few clinical studies available on the use of tacalcitol (EL 3).
 Topical use of vitamin D₃ derivatives (tacalcitol) has been shown to have synergistic effects with systemic cyclosporine in the treatment of severe psoriasis (EL 3).
 Local therapy with vitamin D₃ derivatives is generally well tolerated by the patient and feasible for doctors and patients. Use may be limited by potential transitory skin irritation, especially in treatment of the face or intertriginous zones.

Treatment recommendation

Vitamin D₃ derivatives are recommended for use in induction therapy for mild to moderate psoriasis. ↑↑

Combination therapy with vitamin D₃ derivatives and steroids is recommended in the first four weeks as induction therapy for mild to moderate psoriasis. ↑↑

Phototherapy

Table 7 Summary table

Phototherapy	
Approval in Germany	Clinical experience >50 years depending on modality
Recommended control parameters	Regular inspection of the skin (especially for dermatitis solaris)
Recommended initial dosage	Individual dosage based on skin type, alternatively: UVB: 70% of minimal erythema dose (MED) Oral PUVA: 75% of minimal phototoxic dose (MPD) Bath/cream PUVA: 20–30% minimal phototoxic dose (MPD)
Recommended maintenance dosage	Increase depending on erythema
Onset of clinical effect	After 1–2 weeks
Response rate	UVB: 50–75% of patients achieve PASI 75 after 4–6 weeks (EL 2) PUVA: 75–100% of patients achieve PASI 75 after 4–6 weeks (EL 2)
Main contraindications	Photodermatoses/photosensitivity, skin cancer, immunosuppression Only PUVA: pregnant or nursing women
Important UAEs	Erythema, itching, blistering, malignancy Only oral PUVA: nausea
Important drug interactions	Important note: photosensitizing drug
Misc.	Combination with topical preparations has synergistic effects; phototherapy should not be combined with cyclosporine A

Instructions for application	
<u>Pre-treatment procedures</u>	
– The treating physician should conduct a thorough inspection of the entire body surface, especially for signs of cancerous lesions, precancerous lesions, and dysplastic nevus cell nevi.	
– The patient should be informed about the course of therapy, possible side effects, and potential long-term risks – in particular the increased risk of cancer as a result of therapy. He or she should be made aware of synergistic effects resulting from additional UV exposure during leisure time or self-treatment.	
– Before beginning oral PUVA therapy, the patient should be examined by an ophthalmologist. Protective goggles should also be obtained.	
<u>Measures during therapy</u>	
– The UV dose must be precisely recorded (J/cm ² or mJ/cm ²). Erythema development must be controlled regularly before increasing the dosage.	
– Regular monitoring of therapy also includes documentation of the success of therapy, side effects, and any concomitant therapy use.	
– Protective goggles should be worn during UV light therapy.	
– Unless they are the focus of therapy, chronic sun exposed areas (face, neck, backs of the hands) and genital regions should be protected from exposure to UV light.	
– Adequate protective measures against exposure to sunlight are necessary during therapy.	
<u>Post-therapy measures</u>	
– After completing a treatment series, the cumulative UV dosage and the number of treatment sessions must be recorded and given to the patient.	
– Patients with a high cumulative UV dose should undergo lifelong regular skin cancer screening.	

Summary evaluation
For monotherapy, 35 studies on UV phototherapy [64,47,125,139,240,201,161,34,67,172,11,109,129,141,54,175,189,181,16,130,52,69,8,13,114,135,106,133,72,48,23,24,174,88,197], 38 on PUVA therapy [27,76,83,138,171,204,197,7,238,10,220,200,105,101,18,25,28,52,107,108,169,92,190,14,44,45,29,195,170,68,215,89,218,26,191,228,233,221], and 10 studies on laser therapy [87,102,217,61,96,99,58,72,48,211] met the inclusion criteria of the guidelines. 50 - 75 % of patients treated with UVB phototherapy achieved at least a 75 % improvement in PASI score after four to six weeks and often there was complete clearance of lesions (EL 2). Some 75 - 100 % of all patients treated with PUVA therapy achieve at least a 75 % improvement in PASI score after four to six weeks, and complete clearance of lesions is common (EL 2). Dermatitis solaris, as a result of overdose, is by far the most commonly reported adverse effect, and is also frequently reported. For repeated or long-term therapy, the consequences of high cumulative UV dosages, such as premature aging of the skin, must be taken into account. There is also a risk of developing cancer which has been shown for oral PUVA and is considered likely for local PUVA and UVB. The feasibility of therapy for the doctor is considerably limited by the need for space, financial considerations, and personnel/time. For the patient, feasibility it is significantly limited by the amount of time involved. The cost-to-benefit ratio for phototherapy is good from the perspective of health insurers. Yet the cost and time involved for the patient are potentially considerable.

Treatment recommendation	
UVB and PUVA are recommended for induction therapy for moderate to severe psoriasis vulgaris, especially if there is involvement of a large body surface area.	↑↑
Despite the superior efficacy of PUVA compared with UVB therapy alone, narrow band UVB therapy may be considered as the first choice for phototherapy. Feasibility is better and there is a lower risk of malignancy.	↑
The use of excimer laser may be recommended for targeted therapy of individual psoriatic plaques.	↑
The combination with topical vitamin D ₃ derivatives may be recommended for improving the response rate.	↑
The customary combination with dithranol and steroids may be recommended based on clinical experience, but not on the basis of the available data.	↑
Given low feasibility and an association with long-term adverse effects due to the cumulative UV dose, long-term phototherapy is not advisable.	↓

Evaluation of systemic therapies

Adalimumab

Table 8 Summary table

Adalimumab	
Approval in Germany	2005 (psoriatic arthritis) 2007 (plaque psoriasis)
Recommended control parameters	Exclude tuberculosis before treatment initiation; during therapy: blood count, liver values, clinical signs of infection
Recommended initial dosage	80 mg subcutaneously
Recommended maintenance dosage	40 mg subcutaneously every 2 weeks
Onset of clinical effect	Four to eight weeks; maximum efficacy at 16 weeks
Response rate	PASI 75 achieved in 71–80% of patients with moderate to severe psoriasis (EL 1)
Main contraindications	Chronic infections, tuberculosis, cardiac insufficiency (NYHA class III/IV)

Table 8 continued

Adalimumab	
Important UAEs	Reactions at the injection site, serious infections, hair loss, autoimmune phenomena
Important drug interactions	Anakinra, abatacept
Misc.	–

Instructions for application
<u>Pre-treatment procedures</u>
– Rule out acute infection
– Definitive exclusion of tuberculosis as per current recommendations of the Paul Ehrlich Institute [51], see Appendix 1
– If warranted by patient history or clinical or laboratory chemical tests, HIV and viral hepatitis should be excluded.
– Contraception must be ensured and pregnancy ruled out in women of child-bearing age
– Patients should be informed that serious infections have occurred with use of the drug and that prompt medical attention is required if infection is suspected.
<u>Measures during therapy</u>
– Surveillance for infection; if there is suspected infection, therapy should be discontinued, at least temporarily.
<u>Post-therapy measures</u>
– None

Table 9 Monitoring

Months	→	Before	1	3	Every 2 - 3 months
Diagnosis ↓					
Blood differential		X	X	X	X
ASAT, ALAT, γGT		X	X	X	X
Pregnancy test (urine)		X			
For suspected infection, see pre-treatment procedures					

Summary evaluation
Seven of the nine evaluated studies met the criteria for inclusion in the guidelines. [75,146,165,186,196,226,21,231]
This includes two studies from the research conducted for the European S3 psoriasis guideline. Some 71 - 80 % of patients with moderate to severe psoriasis who are treated with adalimumab (initial dose of 80 mg given subcutaneously, followed by 40 mg every other week) achieve at least PASI 75 after 12-16 weeks (EL 1).
During the induction phase, adalimumab is one of the most highly effective medications for the treatment of psoriasis vulgaris. Adalimumab is suitable for long-term therapy.
In patients with concomitant psoriatic arthritis, administration of TNF-α antagonists is especially useful. Various safety aspects related to the use of should be recalled. Foremost among these is the risk of serious infection. This requires careful assessment of the indications for therapy, as well as education and monitoring of the patient.
Given the vast numbers of patients who have been treated with adalimumab (including for diseases other than psoriasis), the risk of adverse effects is readily evaluated.
Therapy is feasible for the doctor and patient. Combination therapy with MTX and adalimumab could also counteract the formation of antibodies to the drug, as has been seen with the use of MTX and infliximab.

Treatment recommendation
Adalimumab is recommended for induction therapy in patients with moderate to severe plaque psoriasis, especially if other forms of therapy have failed, are not tolerated, or are contraindicated.
↑↑

Cyclosporine

Table 10 Summary table

Cyclosporine	
Approval in Germany	1983 (transplantation medicine) 1993 (psoriasis vulgaris)
Recommended control parameters	See below
Recommended initial dosage	2.5–3 (max. 5) mg/kg body weight
Recommended maintenance dosage	Interval therapy (8–16 weeks) with a dosage reduction at the end of induction therapy (e.g., 0.5 mg/kg body weight every 14 days) or Continuous long-term therapy with dosage reduction, e.g., 50 mg every 4 weeks after week 12 and increasing the dosage by 50 mg if relapse occurs Maximum 2 years treatment duration
Onset of clinical effect	After about 4 weeks
Response rate	Dose-dependent, after 8–16 weeks at 3 mg/kg body weight, PASI 75 in 50–70% (EL 1)
Main contraindications (limited selection)	Absolute contraindications: Relevant kidney dysfunction Uncontrolled arterial hypertension Uncontrolled infection Relevant malignancy (current or past, especially hematological diseases and cutaneous malignancies with the exception of basal cell carcinoma) Relative contraindications: Relevant liver dysfunction Pregnancy and lactation Concomitant use of substances that interact with cyclosporine Simultaneous light therapy or PUVA pre-therapy with a cumulative dose >1,000 J/cm ² Concomitant use of other immunosuppressants, retinoids, or long-term pre-therapy with MTX
Important UAEs	Renal dysfunction, increased blood pressure, liver dysfunction, nausea, loss of appetite, vomiting, diarrhea, hypertrichosis, gingival hyperplasia, tremors, fatigue, paresthesia

Table 10 continued

Cyclosporine	
Important drug interactions (limited selection)	Increase of the cyclosporine level (CYP3A inhibition) through: Allopurinol, calcium antagonists, amiodarone, antibiotics (macrolides, clarithromycin, josamycin, ponsinomycin, pristinamycin, doxycycline, gentamicin, tobramycin, ticarcillin, quinolones), ketoconazole, oral contraceptives, methylprednisolone (high dosages), ranitidine, cimetidine, grapefruit juice Decrease of the cyclosporine level (CYP3A induction) through: Carbamazepine, phenytoin, barbiturates, metamizole, St. John's wort Possible reinforcement of nephrotoxic adverse drug reactions through: Aminoglycosides, amphotericin B, ciprofloxacin, acyclovir, non-steroidal antiphlogistics Specific interactions: Potassium-saving substances: increased risk of hyperpotassämia Reduced clearance of: Digoxin, colchicine, prednisolone, HMG-CoA reductase inhibitors (e.g. lovastatin), diclofenac
Misc.	In transplant patients, increased risk of lymphoproliferative diseases In psoriasis patients excessive light therapy can lead to increased risk of squamous cell cancer Only moderately effective against psoriatic arthritis and not approved Also been used successfully in children with chronic inflammatory diseases

Instructions for applicationPre-treatment procedures

General measures

- Patient history including past and current diseases (e.g., severe infections, malignancy, kidney or liver diseases), accompanying medication (see drug interactions in long version [152]).

Specific measures

- With corresponding patient history or clinical or laboratory signs, HIV infection and viral hepatitis should be excluded.
- Inspection for potentially malignant skin lesions.
- Signs of existing infection
- Take blood pressure measurements at two different times.

Patient education:

- Patients should be made aware that any infection may be more severe or have a typical symptoms and course and they must therefore seek prompt medical attention.
- Drug interactions (also inform other treating physicians of therapy)
- Ensure contraception and rule out pregnancy in women of childbearing age (important note: diminished efficacy of progesterone-based contraceptive drugs)
- Avoid excessive exposure to sunlight, use of sun protection

Measures during therapy

Interview / examination

- Status of skin and mucous membranes (e.g., increased body hair, swollen gums, rule out skin cancer)
- Signs of existing infection
- Gastrointestinal symptoms and neurological symptoms
- Repeat recommendation to protect against exposure to sunlight
- Check co-medication
- Measure blood pressure
- In uncomplicated low-dose long-term therapy (2.5 -3mg/kg body weight daily) later 2-month control intervals maybe used
- Shorter intervals, e.g., in patients with risk factors, when increasing dosage, with the use of metabolic drugs or drugs with potential interactions
- Creatinine clearance if the creatinine plasma levels appear abnormal
- In certain patients undergoing intermittent or short-term therapy, a smaller number of controls (e.g., regular control of blood pressure and creatinine values) may be sufficient
- Assessment of cyclosporine levels may occasionally be wise especially with suspected non-compliance or toxicity due to drug interactions

Post-therapy measures

- None

Table 11 Monitoring

Weeks	→	Before	2	4	8	12	16
Diagnosis ↓							
Blood count ^a		X	X	X	X	X	X
Liver values ^b		X	X	X	X	X	X
Electrolytes ^c		X	X	X	X	X	X
Serum creatinine		X	X	X	X	X	X
Uric acid		X		X	X	X	X
Pregnancy test (urine)		X					
Cholesterol, triglycerides ^d		X		X		X	
Magnesium ^e		X		X		X	

^a Erythrocytes, leukocytes, thrombocytes + blood differential^b Transaminase, γGT, bilirubin^c Sodium, potassium^d Assess twice if possible (empty stomach) and additionally at week -2 and week 0^e Only if indicated (e.g., muscle cramps)

Summary evaluation
 Of the studies evaluated on cyclosporine therapy in psoriasis patients, 28 meet the criteria for inclusion in the guidelines. [56,113,55,57,119,62,94,143,213,39,239,207,91,120,71,160,63,93,65,129,137,185,176,230,67,82,1,2] This includes 15 studies from the research for the European S3 psoriasis guidelines. After 12-16 weeks, 50 - 70 % patients achieve PASI 75 (EL 1). Cyclosporine is especially suitable for induction therapy. In long-term therapy, after one to two years maximum, continuation of therapy should be carefully considered given potential side effects, especially nephrotoxicity and increased blood pressure as well as the increased risk of cancer. Given the large number of patients who have been treated with cyclosporine (for other diseases as well), the risk of undesirable adverse effects is predictable. Various drug interactions can occur with the use of cyclosporine, on the one hand leading to altered availability of cyclosporine or the concomitant drug and on the other hand increasing the risk of adverse effects. Combination use with topical preparations is helpful in the treatment of plaque psoriasis, especially since it appears that concomitant local therapy with vitamin D₃ analogues or steroids can help reduce cyclosporine dosage without diminishing its effectiveness.

Treatment recommendation
 Cyclosporine may be recommended, especially for induction therapy, in patients with moderate to severe psoriasis vulgaris. ↑
 Combination therapy with cyclosporine and topical preparations in the treatment of psoriasis vulgaris may be recommended. ↑

Instructions for application
Pre-treatment procedures
General measures
 – Rule out acute infection
 – Exclude TB based on current recommendations by the Paul Ehrlich Institute [51], see Appendix 1
 – If warranted by the patient history or the results of clinical or laboratory tests, rule out HIV infection and viral hepatitis.
Specific measures
 – Patients must ensure adequate contraception / rule out pregnancy in women of childbearing age
 – Patients should be informed of the potential for severe and atypical infections and should seek prompt medical attention if symptoms occur.
Measures during therapy
 – Monitoring for infections; if an infection is detected or suspected, stop therapy at least temporarily
 – Discontinue therapy if pregnancy occurs
Post-therapy measures
 – None

Etanercept

Table 12 Summary table

Etanercept	
Approval in Germany	2002 (psoriatic arthritis)/2004 (psoriasis vulgaris)/2008 (psoriasis vulgaris in children)
Recommended control parameters	Blood count, liver values
Recommended initial dosage	2 × 25, 1 × 50 or 2 × 50 mg/weekly
Recommended maintenance dosage	2 × 25 mg/weekly, 1 × 50 mg/weekly
Onset of clinical effect	After 6–12 weeks; maximum efficacy after 24 weeks
Response rate	PASI 75 in 34% (2 × 25 mg), 38% (1 × 50 mg) and 49% (2 × 50 mg) after 12 weeks (EL 1)
Main contraindications	Infections, pregnancy, nursing
Important UAEs	Local reaction, infections
Important drug interactions	Anakinra (IL-1 receptor antagonist), abatacept (co-stimulation inhibitor)
Misc.	–

Table 13 Monitoring

Months	→	Before	1	3	6	8
Diagnosis ↓						
Blood differential		X	X	X	X	X
ALAT, ASAT, γGT		X	X	X	X	X
Pregnancy test (urine)		X				
If there is suspicion of infection, see pre-treatment procedures.						

Summary evaluation
 Out of 20 studies assessed in regard to the efficacy of etanercept monotherapy in patients with psoriasis, 16 met the criteria for inclusion. [80,128,46,168,227,219,36,149,70,109,110,241,224,17,32,31] This includes eight studies from the research for the European S3 psoriasis guideline. In treatment with etanercept 2 x 25 mg or 1 x 50 mg given subcutaneously once a week, about 35 % or 38 % of patients achieve PASI 75 after 12 weeks. For therapy with 2 x 50 mg given subcutaneously every week for 12 weeks, about 50 % of patients achieve PASI 75 (EL 1). The maximum efficacy of etanercept is not reached until after the induction phase. Etanercept is suitable for long-term use. Based on the data from available studies, an increase in effectiveness in long-term therapy of psoriasis vulgaris may be expected in some patients. The use of TNF-α antagonists is especially beneficial for patients with psoriatic arthritis. The efficacy and safety of etanercept are not influenced by the formation of antibodies to the drug. Various safety aspects should be considered when administering etanercept. One of the most important is the risk of infection. Careful evaluation of the indications for use of the drug as well as education and monitoring of the patient are essential. Given the widespread use of etanercept (for other diseases as well), the risk of side effects related to its use is readily assessed. Therapy is feasible for the doctor and patient. Combination use of etanercept with MTX or acitretin can have synergistic effects.

Treatment recommendations
 Etanercept 2x50 mg is recommended for induction therapy in patients with moderate to severe psoriasis vulgaris, especially if other treatment forms have been unsuccessful, are not tolerated, or are contraindicated. ↑↑
 Etanercept 1 x 50 mg or 2 x 25 mg may be recommended for induction therapy. ↑
 Comment: In the framework of the consensus conference, there was no strong consensus (>75 %) on the therapy recommendations for etanercept. The recommendation was based on a majority vote of 62 % of the guidelines experts. Alternative formulations were "may be recommended" (2 x 50 mg) or "may be considered" (1 x 50 or 2 x 25). This was due to the initially comparatively lower efficacy of etanercept versus other biological agents, given that etanercept reaches maximum efficacy only after the induction phase.

Fumaric acid esters

Table 14 Summary table

Fumaric acid esters	
Approval in Germany	1995 (psoriasis vulgaris, moderate to severe disease)
Recommended control parameters	Serum creatinine, transaminase/ γ GT, blood differential, urine status
Recommended initial dosage	Based on recommended dosage scheme
Recommended maintenance dosage	Individual dosage modification
Onset of clinical effect	After about 6 weeks
Response rate	PASI 75 in 50–70% of patients at the end of the induction phase after 16 weeks (EL 2)
Main contraindications	Chronic diseases of the gastrointestinal tract and/or kidneys as well as chronic diseases that are associated with diminished leukocyte count or function Patients with malignant diseases Pregnant or nursing women
Important UAEs	Gastrointestinal complaints, flush, lymphopenia, eosinophilia
Important drug interactions	No known drug interactions
Misc.	–

Table 15 Dosing scheme for fumaderm therapy

	Fumaderm [®] initial	Fumaderm [®]
Week 1	1-0-0	
Week 2	1-0-1	
Week 3	1-1-1	
Week 4		1-0-0
Week 5		1-0-1
Week 6		1-1-1
Week 7		2-1-1
Week 8		2-1-2
Week 9		2-2-2

Instructions for applicationPre-treatment procedures

– Laboratory controls see Table 16

Measures during therapy

– Laboratory controls see Table 16

Post-therapy measures

– None

Table 16 Monitoring

Weeks Diagnosis ↓	→	Before	Up to 4th month every 4 weeks	After 4th month every 8 weeks
Blood differential ^a		X	X	X
Liver values ^b		X	X	X
Serum creatinine		X	X	X
Urine status		X	X	X

^aErythrocytes, leukocytes, thrombocytes, blood differential^bTransaminase, γ GT**Summary evaluation**

Out of 13 evaluated studies, nine met the criteria for inclusion in the guidelines. [6,111,158,5,15,33,132,151,73] After 16 weeks, 50 - 70 % of patients achieved PASI 75 (EL 2).

Fumaric acid esters are suitable for long-term therapy.

The clinical experience with fumaric acid esters is much greater than the documentation of efficacy and safety of their use in clinical studies.

Clinical use of the drug is limited by gastrointestinal effects and symptoms of flush. The feasibility for the doctor and patient is good.

An advantage of fumaric acid esters is their low rate of drug interactions.

Treatment recommendation

Fumaric acid esters may be recommended for induction therapy in adult patients with moderate to severe psoriasis vulgaris.



Infliximab

Table 17 Summary table

Infliximab	
Approval in Germany	2004 (psoriatic arthritis)/2005 (psoriasis vulgaris)
Recommended control parameters	Before therapy rule out tuberculosis, during therapy: leukocyte and thrombocyte counts, liver values, clinical signs of infection
Recommended initial dosage	5 mg/kg of body weight
Recommended maintenance dosage	5 mg/kg of body weight (initially: infusions on day zero, week two and week six; maintenance therapy: every 8 weeks)
Onset of clinical effect	After 1–2 weeks
Response rate	PASI 75 in \geq 80% in patients with moderate to severe psoriasis vulgaris (EL 1)
Main contraindications	Acute or chronic infections, tuberculosis, cardiac insufficiency NYHA III–IV
Important UAEs	Infusion reactions, severe infections, autoimmune phenomena
Important drug interactions	Anakinra
Misc.	–

Instructions for application	
<u>Pre-treatment procedures</u>	
<ul style="list-style-type: none"> - Exclude acute infection - Certain exclusion of tuberculosis based on current recommendations of the Paul Ehrlich Institute [51], see Appendix 1 - If warranted by the patient history or clinical or laboratory chemical signs, rule out HIV infection or viral hepatitis. - Reliable contraception / rule out pregnancy in women of childbearing age - Patients should be informed of the potential for severe and atypical infections and should seek prompt medical attention if symptoms occur. 	
<u>Measures during therapy</u>	
<ul style="list-style-type: none"> - Monitoring of the patient up to one hour after infusion - Monitoring of the patient for infections; if infection is suspected, treatment should be interrupted 	
<u>Post-therapy measures</u>	
<ul style="list-style-type: none"> - None 	

Table 18 Monitoring

Months Diagnosis ↓	→	Before	1	2	3
Blood differential		X	Before each additional infusion		
ASAT, ALAT, γGT		X	Before each additional infusion		
Pregnancy test (urine)		X			
For suspected infections, see pre-treatment procedures					

Summary evaluation
<p>Out of 15 evaluated studies, nine studies on monotherapy met the criteria for inclusion in the guidelines. [9,78,184,203,145,40,199,126,38] This includes six studies from the research for the European S3 Psoriasis guideline.</p> <p>After 10 weeks of infliximab therapy (5 mg/kg of body weight at the usual intervals), 75 - 88 % of patients with moderate to severe psoriasis achieve PASI 75 (EL 1). Infliximab is one of the most effective treatments available for induction therapy in psoriasis vulgaris. Infliximab is also suitable for long-term therapy. Based on data from available studies, the efficacy of long-term therapy may diminish in some psoriasis patients after 24 weeks of treatment. The use of TNF-α antagonists can be especially useful in patients with psoriatic arthritis. There are also indications that infliximab may be suitable for the treatment of severe, rare forms of psoriasis. Several safety aspects must be taken into consideration for the use of infliximab. The most important are infusion reactions and the risk of serious infection. This requires a careful assessment of the indications for its use, and thorough education and monitoring of the patient.</p> <p>Given the vast number of patients who have been treated with infliximab (for other diseases as well), the risk of adverse effects is readily assessed. The feasibility for the patient is good. For the doctor, the effort involved is increased by the need for infusion management.</p> <p>Therapy should be given continuously every eight weeks in order to prevent more frequent infusion reactions as can occur with episodic administration.</p> <p>Combination therapy with infliximab and MTX may help prevent the formation of antibodies.</p>

Treatment recommendation
<p>Infliximab is recommended for induction therapy in patients with moderate to severe psoriasis vulgaris, especially if other forms of therapy have failed to achieve sufficient treatment success or are contraindicated or not tolerated.</p>

Methotrexate

Table 19 Summary table

Methotrexate	
Approval in Germany	
Lantarel [®]	1991 (psoriasis vulgaris)
Metex [®] 7.5/10 mg	1992 (psoriasis vulgaris)
Metex [®] 2.5 mg	2004 (psoriasis vulgaris)
Recommended control parameters	Blood differential (Hb, Hct, blood differential, thrombocytes), kidney function (serum creatinine, urea, urine sediment), liver values (serum transaminase), amino-terminal propeptide of type III pro-collagen
Recommended initial dosage	7.5–15 mg/weekly
Recommended maintenance dosage	5–22.5 mg/weekly depending on effect
Onset of clinical effect	After 4–8 weeks
Response rate	PASI 75 in 25–50% of patients at the end of the induction phase of 16 weeks (EL 2)
Main contraindications	Liver dysfunction, pregnancy
Important UAEs (limited selection)	Liver fibrosis/cirrhosis, pneumonia/ alveolitis, bone marrow depression, renal damage, alopecia (reversible), nausea, weariness, vomiting, elevated transaminases, infection, gastrointestinal ulcerations, nephrotoxicity
Important drug interactions (limited selection)	Cyclosporine, salicylates, sulfonamides, probenecide, penicillin, colchicin, NSAIDs (naproxene, ibuprofene, etc.), ethanol, co-trimoxazole, pyrimethamine, chloramphenicol, sulfonamides, prostaglandin synthesis inhibitors, cytostatics, probenecide, barbiturates, phenytoin, retinoids, sulfonamides, sulfonylurea, tetracyclines, co-trimoxazol, chloramphenicol, dipyridamole, retinoids, ethanol, leflunomide
Misc.	Strict avoidance of alcohol, chest X-ray before treatment initiation

Instructions for application	
<u>Pre-treatment procedures</u>	
General measures	
<ul style="list-style-type: none"> – Rule out acute infection – If warranted based on patient history or clinical or laboratory signs, rule out HIV infection and viral hepatitis. 	
Specific measures	
<ul style="list-style-type: none"> – Inform the patient on how to take the drug (only one day a week) and about early symptoms of potential adverse effects – Physical examination, detection of skin changes typical of cirrhosis – Liver ultrasound if needed, i.e., if there is a positive history or with detection of pathology during physical inspection – Chest x-ray (for comparison later if any pulmonary changes occur during therapy) – Measure serum levels of amino-terminal propeptide type III procollagen (PIIINP) before beginning treatment. 	
<u>Measures during therapy</u>	
<ul style="list-style-type: none"> – Contraception (women as well as men undergoing treatment) – Laboratory controls, see Table 20 – More frequent laboratory tests are needed when increasing dosage and in patients with an increased risk of elevated MTX levels (dehydration, diminished renal function, new drugs) – Chest x-ray: with symptoms of acute fever, cough, dyspnea, and cyanosis; important: MTX alveolitis – MTX may be given with supplemental folates to reduce drug toxicity. A common treatment scheme is folate 5 mg the day after taking MTX. 	
<u>Post-therapy measures</u>	
<ul style="list-style-type: none"> – Strict contraception for at least three months after therapy (men and women) 	

Table 20 Monitoring

Weeks Diagnosis ↓	→	Before treatment	1st month: 1 x/weekly	2nd - 3rd month: 1 x every 4 weeks	From 4th month on- ward: every 2 - 3 months
Blood differential ^a	X	X	X	X	X
Liver values ^b	X	X	X	X	X
Creatinine	X	X	X	X	X
Pregnancy test (urine)	X				
Liver ultrasound	X	°			
Chest x-ray	X				
Amino-terminal propeptide type III procollagen	X		°		

^aHb, Hct, erythrocytes, leukocytes, blood differential, thrombocytes

^bALAT, ASAT; AP, γGT, albumin, bilirubin, LDH

^cOnce yearly for dosages ≥15 mg/week

^dBefore treatment and every three months in 1st year, then 1x a year if available

Summary evaluation
In regard to the efficacy of methotrexate therapy in patients with psoriasis vulgaris 14 studies met the criteria for inclusion in the guidelines. [93,159,234,41,97,186,196,182,65,226,193,241,11,150,172] This includes six studies from the research for the European S3 psoriasis guideline. After 16 weeks of treatment with MTX 25 - 50 % of patients achieve PASI 75 (EL 2). The maximum efficacy of MTX is not reached until after the induction phase, regardless of dosing scheme. MTX is suitable for long-term therapy. The clinical experience with methotrexate is much greater than the documentation of its effectiveness and safety in clinical studies. Clinical use of the drug is limited by severe adverse effects associated with its use as well as very rare, but serious idiosyncrasies. Careful patient selection, thorough education of the patient, strict monitoring, use of the lowest possible effective dose (max. 22.5 mg/week), and additional use of folic acid or folinic acid allows for an acceptable safety profile for MTX. Feasibility for the doctor and patient is limited by the need for careful monitoring of the patient during the induction phase. Injection therapy is preferable due to individually variable bioavailability of orally administered MTX. MTX is suitable for use with TNF-α inhibitors. MTX may also be used in patients with concomitant psoriatic arthritis. Of all systemic agents, MTX has the lowest medication costs per day.

Treatment recommendation
MTX may be recommended for induction therapy in patients with moderate to severe psoriasis vulgaris. 

Retinoids

Table 21 Summary table

Acitretin	
Approval in Germany	1992 (Psoriasis vulgaris)
Recommended control parameters	Blood count, liver values, kidney values, blood lipids, glucose (initial), pregnancy test, X-ray controls of bone status in patients undergoing long-term therapy
Recommended initial dosage	0.3–0.5 mg/kg of body weight/daily for about 4 weeks, possibly followed by 0.5–0.8 mg/kg of body weight
Recommended maintenance dosage	Individual dosage depending on result and tolerability
Onset of clinical effect	After 4–8 weeks
Response rate	Highly variable and dose-dependent, partial remission (PASI 75) in 20–30% of patients (30–40 mg/daily) (EL 2)
Main contraindications	Kidney and liver damage, women of childbearing age who plan to have children, pregnancy, nursing
Important UAEs	Hypervitaminosis A, e.g., cheilitis, xerosis, nosebleed, alopecia, increased vulnerability of the skin
Important drug interactions	Phenytoin, tetracycline, methotrexate, alcohol, minipill
Misc.	Contraception up to 2 years after discontinuing the drug in women of childbearing age

Instructions for application	
<u>Pre-treatment procedures</u>	
<ul style="list-style-type: none"> – Rule out alcohol misuse – Inform the patient that blood may not be donated during therapy and for up to one year afterward – Ask about bone and joint pain – Laboratory controls, see Table 22 	
<u>Measures during therapy</u>	
<ul style="list-style-type: none"> – For long-term therapy (1–2 years): if symptoms warrant, exclude ossification by radiological examination of the spine and joints. – For women of childbearing age: adequate contraception and avoidance of alcohol during treatment – Laboratory controls, see Table 22 	
<u>Post-therapy measures</u>	
<ul style="list-style-type: none"> – Advise patients not to donate blood for up to one year after stopping therapy – Women of childbearing age must ensure effective contraception for up to two years after therapy – Women of childbearing age should avoid alcohol consumption for up to two months after ending treatment 	

* The use of two contraceptive measures is advised: e.g., condom + pill; contraceptive coil/NuvaRing + pill. Important: avoid the use of low-dose progesterone preparations (minipill) during treatment and for 2 years after stopping treatment as their effectiveness is diminished by acitretin

Table 22 Monitoring

Weeks Diagnosis ↓	→	Before treatment	1	2	4	8	12	16
Blood differential ^a		X				X		X
Liver enzymes ^b		X			X	X		X
Kidney values ^c		X						
Triglycerides, cholesterol, HDL ^d		X			X			X
Pregnancy test (urine) (monthly up to 2 years after therapy)		X			monthly			
Glucose (empty stomach)		X						

^a Simple blood count (Hb, Hct, leukocytes, thrombocytes)

^b ASAT, ALAT, AP, γ GT

^c Creatinine, urea

^d Preferably measured twice on an empty stomach (2 weeks before and on the day of treatment initiation)

Summary evaluation

Out of 59 studies evaluated, eight meet the criteria for inclusion in the guidelines. [117,86,26,147,32,70,59,222] This includes studies on monotherapy and combination therapy (EL 2). Seven studies were included from the research for the European S3 Psoriasis Guidelines. The effectiveness of low-dose retinoids as monotherapy in moderate to severe psoriasis vulgaris is not satisfactory. After eight to 12 weeks, at a dosage of 0.4mg/kg of body weight to max. 40mg/daily, 23 - 30 % of patients achieve PASI 75 (EL 2). Although the drug is more effective at higher dosages, the related side effects are also often greater, with involvement of the skin and mucous membranes.

Use of the drug is limited in women of childbearing age due to the risk of birth defects, the need for monthly pregnancy tests, and having to ensure contraception for up to two years after stopping therapy.

One advantage of retinoids is their synergistic effects when used in combination with UV phototherapy. The data from the included studies are insufficient, however. The results of a paper by Gisondi et al. suggest potential synergistic effects in combination therapy with retinoids and TNF inhibitors, but larger studies are still needed.

Treatment recommendation

Due to its lacking efficacy, acitretin cannot be recommend as low-dose monotherapy. ↓

Acitretin cannot be recommended for women of childbearing age with plaque psoriasis. ↓

Ustekinumab

Table 23 Summary table

Ustekinumab	
Approval in Germany	January 2009 (psoriasis vulgaris)
Recommended control parameters	In week four, then every 8–12 weeks: blood count and differential, GOT, GPT, γ GT
Recommended Initial dosage	45 mg (for >100 kg body weight: 90 mg) in weeks 0 and 4

Table 23 continued

Ustekinumab	
Recommended maintenance dosage	45 mg (for >100 kg body weight: 90 mg) every 12 weeks
Onset of clinical effect	Six to 12 weeks; maximum efficacy after 24 weeks
Response rate	PASI 75 after 12 weeks 45 mg: 67% (EL 1) (PASI 75 after 12 weeks 45 mg in patients ≤100 kg body weight: 73–74%, PASI 75 after 12 weeks 90 mg in patients >100 kg body weight: 68–71%)
Main contraindications	Active tuberculosis or other serious infectious diseases
Important UAEs	Infections
Important drug interactions	No known interactions
Misc.	–

Instructions for application

Pre-treatment procedures

- Rule out acute infection
- Exclude tuberculosis based on current recommendations of the Paul Ehrlich Institute [51], see Appendix 1
- If warranted by patient history or clinical or laboratory signs, rule out HIV infection and viral hepatitis.
- Contraception must be ensured and pregnancy excluded in women of child-bearing age
- Patients should be informed of the potential for serious and atypical infections and that they should seek prompt medical attention if symptoms occur.

Measures during therapy

- Monitoring for infection, if there is suspicion of infection, therapy should be discontinued, at least temporarily
- Interrupt therapy if pregnancy occurs
- Therapy must be administered by trained medical personnel

Post-therapy measures

- None

Table 24 Monitoring

Months Diagnosis ↓	→	Before	1	2	3
Blood differential		X			Before each injection
ASAT, ALAT, γ GT		X			Before each injection
Pregnancy test (urine)		X			
If infection is suspected, see pre-treatment procedures					

Summary evaluation
 All three of the studies that were evaluated also met the criteria for inclusion in the guidelines. [127,167,77] All were grade A₂ studies, resulting in an evidence level of 1.
 After being treated with ustekinumab 45 mg subcutaneously in weeks 0 and 4, 67 % of patients had at least a 75 % improvement in PASI score after 12 weeks (EL 1).
 Ustekinumab is highly effective against psoriasis vulgaris during the induction phase. In some patients, the maximum effectiveness of the drug is not reached until after six months of treatment. Ustekinumab is suitable for long-term therapy.
 At present, there are data from a few thousand patients. Based on these data, there is no indication of an increased risk of infection. For an assessment of long-term safety, larger patient samples are needed.
 Therapy is feasible for the doctor and patient.

Treatment recommendation
 Ustekinumab is recommended for induction therapy in adult patients with moderate to severe psoriasis vulgaris, especially if other therapies have been unsuccessful, are not tolerated, or are contraindicated. ↑↑

Other therapies

Climatotherapy

Table 25 Summary table

Climatotherapy	
Approval in Germany	More than 200 years of clinical experience with climate therapy
Recommended control parameters	Regular inspections of the skin
Recommended initial dosage	Therapy schemes vary by institution/treatment site
Recommended maintenance dosage	Therapy schemes vary by institution/treatment site
Onset of clinical action	Highly variable
Response rate	Highly variable (EL 3)
Main contraindications	Depend on chosen modality
Important UAEs	Depend on chosen modality
Important drug interactions	N/A
Misc.	–

Summary evaluation
 Out of 39 evaluated studies, two met the criteria for inclusion in the guidelines (EG C). [43,90] The level of evidence is 3.
 During a 1-4 week treatment regime at the Dead Sea, 55 % (two weeks) and 76 % (four weeks) of patients achieved PASI 75 (EL 3).
 For combination therapy with natural phototherapy, the efficacy and safety of treatment are determined by the phototherapy component.
 Climatotherapy is by definition performed in certain regions at specialized clinics.

Treatment recommendation
 Climatotherapy, e.g., at the Dead Sea, may be recommended as part of integrated therapy in patients with a long history of psoriasis vulgaris. ↑
 Climatotherapy is not recommended for acute or short-term therapy. ↓

Psychosocial therapy

Summary evaluation
 Out of nine evaluated studies, three met the criteria for inclusion in the guidelines. [212,66,101] The resulting evidence level is 4.
 The studies on the additive, psychosocial therapy of psoriasis patients were grade B and C studies; there was a significant selection bias and significant dropout rates. These factors make it impossible to draw any valid conclusions at this point on the efficacy of treatment.
 One advantage of psychosocial therapy is the low number of adverse effects.
 Psychosocial therapy in the form of psoriasis symptom management or patient education programs can have direct effects on skin symptoms, e.g., with improved stress management, as well as indirect effects on the development of psoriasis, e.g., with improved adherence / compliance.
 Both of these treatment forms require further empirical study.

Treatment recommendation
 The potential effects of disease on social, emotional, and psychological aspects of life should be considered in any patient with psoriasis. ↑↑
 Patients should be informed of the availability of self-help groups. ↑↑
 Patients should be informed about the possibility of participating in a structured education program according to the recommendations of the Working Group on Dermatological Prevention. ↑↑
 Patients with a severely impaired quality of life, as well as repeated severe exacerbations of psoriasis vulgaris due to stress may be referred, if they wish, to a physician specialized in psychosomatic medicine and psychotherapy or specialized in psychiatry and psychotherapy, or to a psychotherapist or a physician who is also a qualified psychotherapist. ↑↑

Note on use of the guidelines

These guidelines are intended for use by dermatologists in private practice and by clinicians and other specialists involved in the treatment of patients with psoriasis vulgaris. An update of the patient version of the guidelines is currently underway. Finally, the guidelines also provide a guide for health insurers and policy-makers.

The description of selected therapies is intentionally restricted to the most relevant aspects in the opinion of the guidelines' expert committee. Those aspects that are not specific to a certain intervention, such as assessing drug intolerance or allergies, ruling out contraindications, etc. are not listed separately but are instead assumed to be a part of the physician's duty of care.

Physicians are advised to carefully read the package insert and manufacturer information and to determine whether dosage recommendations and other information contained in the guidelines, such as contraindications and drug interactions, is complete and current. Correct dosage and administration are solely the responsibility of the administering physician.

The authors and the publisher kindly ask readers to alert them to any apparent inaccuracies.

Like any science, the field of medicine is in constant flux. Our knowledge of present therapies as well as new treatment options is constantly growing. The utmost care was taken to ensure that the information contained in the guidelines was current at the time of their completion. The

reader is advised to keep abreast of current information after their publication.

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Conflict of interest The documentation and disclosure of potential conflicts of interest was based on the standardized form “Declaration of Conflicts of Interest” provided by the AWMF. The completed forms are available online at <http://www.psoriasis-leitline.de>. Given the diversity of the members of the guidelines group, it is assumed that any potential conflicts of interest balance each other out.

Appendix 1: Measures for excluding tuberculosis (scheme) modified after Diel et al. [51]

(1) Patient history	Immunosuppression Other risk factors for TB Prior LTBI/TB (Occupational) TB contact Origin BCG vaccine status TST/IGRA status Chest X-rays for comparison
(2) Clinical examination	
(3) Chest X-ray in two planes, CT of thorax if needed	If there are radiological signs of prior but inadequately or untreated TB without signs of activity, regardless of results of IGRA test: chemopreventive therapy with isoniazid (INH) for nine months
(4) IGRA test	IGRA negative: generally no chemoprevention IGRA positive: after ruling out the need for therapy: chemopreventive therapy with isoniazid (INH) for nine months
Complementary TST	If previous exposure to someone with infectious pulmonary TB is plausible despite negative IGRA tests and if BCG vaccine is unlikely given the patient’s native country. Or for equivocal results on repeated IGRA test. Positive TST determines further procedures
Bacteriology if needed	

LTBI latent tuberculosis infection, TB tuberculosis, TST tuberculin skin test, IGRA Interferon-Gamma Release Assay

The Interferon-Gamma Release Assay (IGRA) is based on detection of INF- γ , which is secreted by T lymphocytes that are sensitized during a current or previous infection with mycobacterium tuberculosis (MTB).

The two commercially available IGRA tests that are sold in Germany use direct measurement of IFN- γ concentration in whole blood (QuantiFERON-TB[®] Gold In-Tube, Cellestis, Australia; QFT) or measurement of the number of IFN- γ secreting T lymphocytes from isolated peripheral mononucleated cells (PBMC; T-SPOT.TB[®], Oxford Immunotec, Great Britain) [51].

Usually at least one of the tests is offered by routine diagnostic laboratories, or the samples are sent by the lab to one that does offer them. The QuantiFERON-TB[®] Gold In-Tube (QFT) test requires three special tubes coated with antigen which may be obtained from the respective laboratory.

For the T Spot.TB test, 8 ml of fresh, heparinized whole blood are needed from adult patient and at least 2–4 ml from children. Vacutainer Cell Preparation tubes or Standard Lithium Heparin tubes may be used. The sample must then be thoroughly shaken. For both tests, the samples may be transported at room temperature (QuantiFERON-TB[®] within 16 h/T Spot.TB test within 8 h).

For information on outpatient billing, see the resolution of the German Association of Physicians/Health Insurers (Arbeitsgemeinschaft Ärzte/Ersatzkassen), 255th session (written resolution) from 24 September 2010 on the addition of fee number 32670 in section 32.3.7 of chapter 32 of the German Physician Fee Schedule (E-GO) (Resolution No. 930) effective as of 1 January 2011, Dtsch Arztebl 2010; 107(42): A-2069/B-1801/C-1773. For inpatient billing, see OPS Code 1930.0.

References

1. Abe M, Ishibuchi H, Syuto T, Sogabe Y, Yokoyama Y, Ishikawa O (2007) Clinical usefulness and patient satisfaction for treatment with low-dose cyclosporin administration in patients with moderate psoriasis vulgaris. *J Dermatol* 34(5):290–293. doi:10.1111/j.1346-8138.2007.00275.x
2. Abe M, Syuto T, Hasegawa M, Sogabe Y, Yokoyama Y, Ishikawa O (2006) Daily versus intermittent application of high-concentration tacalcitol ointment in combination with low-dose cyclosporin for psoriasis vulgaris. *J Dermatol* 33(2):108–111. doi:10.1111/j.1346-8138.2006.00022.x
3. Agarwal R, Saraswat A, Kaur I, Katare OP, Kumar B (2002) A novel liposomal formulation of dithranol for psoriasis: preliminary results. *J Dermatol* 29(8):529–532
4. Agrup G, Agdell J (1985) A comparison between Antraderm stick (0.5 and 1%) and dithranol paste (0.125 and 0.25%) in the treatment of psoriasis. *Br J Clin Pract* 39(5):185–187
5. Altmeyer P, Hartwig R, Matthes U (1996) Efficacy and safety profile of fumaric acid esters in oral long-term therapy with

- severe treatment refractory psoriasis vulgaris. A study of 83 patients. *Hautarzt* 47(3):190–196
6. Altmeyer PJ, Matthes U, Pawlak F, Hoffmann K, Frosch PJ, Ruppert P, Wassilew SW, Horn T, Kreysel HW, Lutz G et al (1994) Antipsoriatic effect of fumaric acid derivatives. Results of a multicenter double-blind study in 100 patients. *J Am Acad Dermatol* 30(6):977–981
 7. Amornpinyokeit N, Asawanonda P (2006) 8-Methoxypsoralen cream plus targeted narrowband ultraviolet B for psoriasis. *Photodermatol Photoimmunol Photomed* 22(6):285–289. doi:10.1111/j.1600-0781.2006.00249.x
 8. Andrys C, Borska L, Pohl D, Fiala Z, Hamakova K, Krejsek J (2007) Angiogenic activity in patients with psoriasis is significantly decreased by Goeckerman's therapy. *Arch Dermatol Res* 298(10):479–483. doi:10.1007/s00403-006-0723-8
 9. Antoni C, Krueger GG, de Vlam K, Birbara C, Beutler A, Guzzo C, Zhou B, Dooley LT, Kavanaugh A (2005) Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial. *Ann Rheum Dis* 64(8):1150–1157. doi:10.1136/ard.2004.032268
 10. Asawanonda P, Amornpinyokeit N, Nimnuan C (2008) Topical 8-methoxypsoralen enhances the therapeutic results of targeted narrowband ultraviolet B phototherapy for plaque-type psoriasis. *J Eur Acad Dermatol Venereol* 22(1):50–55. doi:10.1111/j.1468-3083.2007.02328.x
 11. Asawanonda P, Nateetongrungsak Y (2006) Methotrexate plus narrowband UVB phototherapy versus narrowband UVB phototherapy alone in the treatment of plaque-type psoriasis: a randomized, placebo-controlled study. *J Am Acad Dermatol* 54(6):1013–1018. doi:10.1016/j.jaad.2006.01.004
 12. Bagatell F (1988) Management of psoriasis: a clinical evaluation of the dermatological patch, Actiderm™, over a topical steroid. *Adv Therap* 5(6):291–296
 13. Bagel J (2009) LCD plus NB-UVB reduces time to improvement of psoriasis vs NB-UVB alone. *J Drugs Dermatol* 8(4):351–357
 14. Barth J, Dietz O, Heilmann S, Kadner H, Kraensel H, Meffert H, Metz D, Pinzer B, Schiller F (1978) Photochemotherapy by 8-methoxypsoralen and UVA in psoriasis vulgaris—clinical experiences in 5 dermatological departments of GDR. *Dermatol Monatsschr* 164(6):401–407 (author's translation)
 15. Bayard W, Hunziker T, Krebs A, Speiser P, Joshi R (1987) Peroral long-term treatment of psoriasis using fumaric acid derivatives. *Hautarzt* 38(5):279–285
 16. Belsito DV, Kechijian P (1982) The role of tar in Goeckerman therapy. *Arch Dermatol* 118(5):319–321
 17. Berends MA, Driessen RJ, Langewouters AM, Boezeman JB, Van De Kerkhof PC, De Jong EM (2007) Etanercept and efalizumab treatment for high-need psoriasis. Effects and side effects in a prospective cohort study in outpatient clinical practice. *J Dermatolog Treat* 18(2):76–83. doi:10.1080/09546630601121086
 18. Berg M, Ros AM (1994) Treatment of psoriasis with psoralens and ultraviolet A. A double-blind comparison of 8-methoxypsoralen and 5-methoxypsoralen. *Photodermatol Photoimmunol Photomed* 10(5):217–220
 19. Berger K, Ehlken B, Kugland B, Augustin M (2005) Cost-of-illness in patients with moderate and severe chronic psoriasis vulgaris in Germany. *J Dtsch Dermatol Ges* 3(7):511–518. doi:10.1111/j.1610-0387.2005.05729.x
 20. Beutner K, Chakrabarty A, Lemke S, Yu K (2006) An intra-individual randomized safety and efficacy comparison of clobetason propionate 0.05% spray and its vehicle in the treatment of plaque psoriasis. *J Drugs Dermatol* 5(4):357–360
 21. Bongiorno MR, Pistone G, Doukaki S, Arico M (2008) Adalimumab for treatment of moderate to severe psoriasis and psoriatic arthritis. *Dermatol Ther* 21(Suppl 2):S15–S20. doi:10.1111/j.1529-8019.2008.00227.x
 22. Brazzelli V, Barbagallo T, Prestinari F, Rona C, De Silvestri A, Trevisan V, Borroni G (2005) Non-invasive evaluation of tacalcitol plus puva versus tacalcitol plus UVB-NB in the treatment of psoriasis: "right-left intra-individual pre/post comparison design". *Int J Immunopathol Pharmacol* 18(4):755–760
 23. Brockow T, Schiener R, Franke A, Resch KL, Peter RU (2007) A pragmatic randomized controlled trial on the effectiveness of highly concentrated saline spa water baths followed by UVB compared to UVB only in moderate to severe psoriasis. *J Altern Complement Med* 13(7):725–732. doi:10.1089/acm.2007.7099
 24. Brockow T, Schiener R, Franke A, Resch KL, Peter RU (2007) A pragmatic randomized controlled trial on the effectiveness of low concentrated saline spa water baths followed by ultraviolet B (UVB) compared to UVB only in moderate to severe psoriasis. *J Eur Acad Dermatol Venereol* 21(8):1027–1037. doi:10.1111/j.1468-3083.2007.02152.x
 25. Buckley DA, Healy E, Rogers S (1995) A comparison of twice-weekly MPD-PUVA and three times-weekly skin typing-PUVA regimens for the treatment of psoriasis. *Br J Dermatol* 133(3):417–422
 26. Caca-Biljanovska NG, V'Lckova-Laskoska MT (2002) Management of guttate and generalized psoriasis vulgaris: prospective randomized study. *Croat Med J* 43(6):707–712
 27. Calzavara-Pinton P (1998) Narrow band UVB (311 nm) phototherapy and PUVA photochemotherapy: a combination. *J Am Acad Dermatol* 38(5 Pt 1):687–690 (pii:S0190-9622(98)70214-2)
 28. Calzavara-Pinton P, Ortel B, Carlino A, Honigsmann H, De Panfilis G (1992) A reappraisal of the use of 5-methoxypsoralen in the therapy of psoriasis. *Exp Dermatol* 1(1):46–51
 29. Calzavara-Pinton PG, Ortel B, Honigsmann H, Zane C, De Panfilis G (1994) Safety and effectiveness of an aggressive and individualized bath-PUVA regimen in the treatment of psoriasis. *Dermatology* 189(3):256–259
 30. Camarasa JM, Ortonne JP, Dubertret L (2003) Calcitriol shows greater persistence of treatment effect than betamethasone dipropionate in topical psoriasis therapy. *J Dermatolog Treat* 14(1):8–13 (pii:EPP1D2VMP79MR4VG)
 31. Campanati A, Goteri G, Simonetti O, Ganzetti G, Giuliadori K, Giuliano A, Sabato S, Stramazotti D, Gulini E, Dusi D, De Blasio S, Fabris G, Offidani A (2009) Angiogenesis in psoriatic skin and its modifications after administration of etanercept: videocapillaroscopic, histological and immunohistochemical evaluation. *Int J Immunopathol Pharmacol* 22(2):371–377
 32. Caproni M, Antiga E, Melani L, Volpi W, Del Bianco E, Fabbri P (2009) Serum levels of IL-17 and IL-22 are reduced by etanercept, but not by acitretin, in patients with psoriasis: a randomized-controlled trial. *J Clin Immunol* 29(2):210–214. doi:10.1007/s10875-008-9233-0
 33. Carboni I, De Felice C, De Simoni I, Soda R, Chimenti S (2004) Fumaric acid esters in the treatment of psoriasis: an Italian experience. *J Dermatolog Treat* 15(1):23–26. doi:10.1080/09541440042000269
 34. Carlin CS, Callis KP, Krueger GG (2003) Efficacy of acitretin and commercial tanning bed therapy for psoriasis. *Arch Dermatol* 139(4):436–442. doi:10.1001/archderm.139.4.436
 35. Carroll CL, Clarke J, Camacho F, Balkrishnan R, Feldman SR (2005) Topical tacrolimus ointment combined with 6% salicylic acid gel for plaque psoriasis treatment. *Arch Dermatol* 141(1):43–46. doi:10.1001/archderm.141.1.43
 36. Cassano N, Loconsole F, Galluccio A, Miracapillo A, Pezza M, Vena GA (2006) Once-weekly administration of high-dosage etanercept in patients with plaque psoriasis: results of a pilot experience (power study). *Int J Immunopathol Pharmacol* 19(1):225–229

37. Cassano N, Miracapillo A, Coviello C, Loconsole F, Bellino M, Vena GA (2006) Treatment of psoriasis vulgaris with the two-compound product calcipotriol/betamethasone dipropionate followed by different formulations of calcipotriol. *Clin Drug Investig* 26(4):227–233
38. Cassano N, Puglisi Guerra A, Malara C, Loconsole F, Galluccio A, Pezza M, Vena GA (2007) Re-induction as a possible alternative modality of dose escalation of infliximab: a prospective evaluation in a small series of psoriatic patients. *Int J Immunopathol Pharmacol* 20(3):647–650
39. Chaidemenos GC, Mourellou O, Avgoustinaki N, Papakonstantinou M, Karakatsanis G, Katsambas A (2007) Intermittent vs. continuous 1-year cyclosporin use in chronic plaque psoriasis. *J Eur Acad Dermatol Venereol* 21:1203–1208
40. Chaudhari U, Romano P, Mulcahy LD, Dooley LT, Baker DG, Gottlieb AB (2001) Efficacy and safety of infliximab monotherapy for plaque-type psoriasis: a randomised trial. *Lancet* 357(9271):1842–1847. doi:10.1016/S0140-6736(00)04954-0
41. Chladek J, Simkova M, Vaneckova J, Hroch M, Chladkova J, Martinkova J, Vavrova J, Beranek M (2008) The effect of folic acid supplementation on the pharmacokinetics and pharmacodynamics of oral methotrexate during the remission-induction period of treatment for moderate-to-severe plaque psoriasis. *Eur J Clin Pharmacol* 64(4):347–355. doi:10.1007/s00228-007-0442-x
42. Chuang TY, Samson CR (1991) Clinical efficacy and safety of augmented betamethasone dipropionate ointment and diflurasone ointment for psoriasis—a multicentre, randomized, double-blinded study. *J Dermatol Treat* 2(2):63–66
43. Cohen AD, Shapiro J, Michael D, Hodak E, Van-Dijk D, Nagan L, Vardy DA (2008) Outcome of “short-term” Dead Sea climatotherapy for psoriasis. *Acta Derm Venereol* 88(1):90–91. doi:10.2340/00015555-0340
44. Collins P, Rogers S (1992) Bath-water compared with oral delivery of 8-methoxypsoralen PUVA therapy for chronic plaque psoriasis. *Br J Dermatol* 127(4):392–395
45. Cooper EJ, Herd RM, Priestley GC, Hunter JA (2000) A comparison of bathwater and oral delivery of 8-methoxypsoralen in PUVA therapy for plaque psoriasis. *Clin Exp Dermatol* 25(2):111–114. doi:ced589[pii]
46. Costanzo A, Mazzotta A, Papoutsaki M, Nistico S, Chimenti S (2005) Safety and efficacy study on etanercept in patients with plaque psoriasis. *Br J Dermatol* 152(1):187–189. doi:10.1111/j.1365-2133.2005.06306.x
47. Coven TR, Burack LH, Gilleaudeau R, Keogh M, Ozawa M, Krueger JG (1997) Narrowband UV-B produces superior clinical and histopathological resolution of moderate-to-severe psoriasis in patients compared with broadband UV-B. *Arch Dermatol* 133(12):1514–1522
48. De Leeuw J, Van Lingen RG, Both H, Tank B, Nijsten T, Martino Neumann HA (2009) A comparative study on the efficacy of treatment with 585 nm pulsed dye laser and ultraviolet B-TL01 in plaque type psoriasis. *Dermatol Surg* 35(1):80–91. doi:10.1111/j.1524-4725.2008.34386.x
49. de Mare S, Calis N, den Hartog G, van Erp PE, van de Kerkhof PC (1988) The relevance of salicylic acid in the treatment of plaque psoriasis with dithranol creams. *Skin Pharmacol* 1(4):259–264
50. Decroix J, Pres H, Tsankov N, Poncet M, Arsonnaud S (2004) Clobetasol propionate lotion in the treatment of moderate to severe plaque-type psoriasis. *Cutis* 74(3):201–206
51. Diel R, Hauer B, Loddenkemper R, Manger B, Kruger K (2009) Recommendations for tuberculosis screening before initiation of TNF-alpha-inhibitor treatment in rheumatic diseases. *Z Rheumatol* 68(5):411–416. doi:10.1007/s00393-009-0475-x
52. Diette KM, Momtaz K, Stern RS, Arndt KA, Parrish JA (1984) Role of ultraviolet A in phototherapy for psoriasis. *J Am Acad Dermatol* 11(3):441–447
53. Douglas WS, Poulin Y, Decroix J, Ortonne JP, Mrowietz U, Gulliver W, Krogstad AL, Larsen FG, Iglesias L, Buckley C, Bibby AJ (2002) A new calcipotriol/betamethasone formulation with rapid onset of action was superior to monotherapy with betamethasone dipropionate or calcipotriol in psoriasis vulgaris. *Acta Derm Venereol* 82(2):131–135
54. Dover JS, McEvoy MT, Rosen CF, Arndt KA, Stern RS (1989) Are topical corticosteroids useful in phototherapy for psoriasis? *J Am Acad Dermatol* 20(5 Pt 1):748–754
55. Elder CA, Moore M, Chang CT, Jin J, Charnick S, Nedelman J, Cohen A, Guzzo C, Lowe N, Simpson K et al (1995) Efficacy and pharmacokinetics of two formulations of cyclosporine A in patients with psoriasis. *J Clin Pharmacol* 35(9):865–875
56. Ellis CN, Fradin MS, Messana JM, Brown MD, Siegel MT, Hartley AH, Rocher LL, Wheeler S, Hamilton TA, Parish TG et al (1991) Cyclosporine for plaque-type psoriasis. Results of a multidose, double-blind trial. *N Engl J Med* 324(5):277–284
57. Engst R, Huber J (1989) Results of cyclosporin treatment of severe, chronic psoriasis vulgaris. *Hautarzt* 40(8):486–489
58. Erceg A, Bovenschen HJ, van de Kerkhof PC, Seyger MM (2006) Efficacy of the pulsed dye laser in the treatment of localized recalcitrant plaque psoriasis: a comparative study. *Br J Dermatol* 155(1):110–114. doi:10.1111/j.1365-2133.2006.07141.x
59. Ezquerra GM, Regana MS, Millet PU (2007) Combination of acitretin and oral calcitriol for treatment of plaque-type psoriasis. *Acta Derm Venereol* 87(5):449–450. doi:10.2340/00015555-0290
60. Fabry H, Yawalkar SJ (1983) A comparative multicentre trial of halometasone ointment and fluocortolone plus fluocortolone caproate ointment in the treatment of psoriasis. *J Int Med Res* 11(Suppl 1):26–30
61. Feldman SR, Mellen BG, Housman TS, Fitzpatrick RE, Geronemus RG, Friedman PM, Vasily DB, Morison WL (2002) Efficacy of the 308-nm excimer laser for treatment of psoriasis: results of a multicenter study. *J Am Acad Dermatol* 46(6):900–906
62. Finzi AF, Mozzanica N, Cattaneo A, Chiappino G, Pigatto PD (1989) Effectiveness of cyclosporine treatment in severe psoriasis: a clinical and immunologic study. *J Am Acad Dermatol* 21(1):91–97
63. Finzi AF, Mozzanica N, Pigatto PD, Cattaneo A, Ippolito F (1993) Cyclosporine versus etretinate: Italian multicentre comparative trial in severe psoriasis. *Dermatology* 187(Suppl 1):8–18
64. Fleischer AB Jr, Clark AR, Rapp SR, Reboussin DM, Feldman SR (1997) Commercial tanning bed treatment is an effective psoriasis treatment: results from an uncontrolled clinical trial. *J Invest Dermatol* 109(2):170–174
65. Flytström I, Stenberg B, Svensson A, Bergbrant IM (2008) Methotrexate vs. ciclosporin in psoriasis: effectiveness, quality of life and safety. A randomized controlled trial. *Br J Dermatol* 158(1):116–121. doi:10.1111/j.1365-2133.2007.08284.x
66. Fortune DG, Richards HL, Kirby B, Bowcock S, Main CJ, Griffiths CE (2002) A cognitive-behavioural symptom management programme as an adjunct in psoriasis therapy. *Br J Dermatol* 146(3):458–465. doi:4622[pii]
67. Franchi C, Cainelli G, Frigerio E, Garutti C, Altomare GF (2004) Association of cyclosporine and 311 nm UVB in the treatment of moderate to severe forms of psoriasis: a new strategic approach. *Int J Immunopathol Pharmacol* 17(3):401–406
68. Frappaz A, Thivolet J (1993) Calcipotriol in combination with PUVA: a randomized double blind placebo study in severe psoriasis. *Eur J Dermatol* 3:351–354

69. Frost P, Horwitz SN, Caputo RV, Berger SM (1979) Tar gel-phototherapy for psoriasis. Combined therapy with suberythemogenic doses of fluorescent sunlamp ultraviolet radiation. *Arch Dermatol* 115(7):840–846
70. Gisondi P, Del Giglio M, Cotena C, Girolomoni G (2008) Combining etanercept and acitretin in the therapy of chronic plaque psoriasis: a 24-week, randomized, controlled, investigator-blinded pilot trial. *Br J Dermatol* 158(6):1345–1349. doi:10.1111/j.1365-2133.2008.08564.x
71. Gisondi P, Del Giglio M, Di Francesco V, Zamboni M, Girolomoni G (2008) Weight loss improves the response of obese patients with moderate-to-severe chronic plaque psoriasis to low-dose cyclosporine therapy: a randomized, controlled, investigator-blinded clinical trial. *Am J Clin Nutr* 88(5):1242–1247
72. Goldinger SM, Dummer R, Schmid P, Prinz Vavricka M, Burg G, Lauchli S (2006) Excimer laser versus narrow-band UVB (311 nm) in the treatment of psoriasis vulgaris. *Dermatology* 213(2):134–139. doi:10.1159/000093852
73. Gollnick H, Altmeyer P, Kaufmann R, Ring J, Christophers E, Pavel S, Ziegler J (2002) Topical calcipotriol plus oral fumaric acid is more effective and faster acting than oral fumaric acid monotherapy in the treatment of severe chronic plaque psoriasis vulgaris. *Dermatology* 205(1):46–53
74. Gollnick H, Menter A (1999) Combination therapy with tazarotene plus a topical corticosteroid for the treatment of plaque psoriasis. *Br J Dermatol* 140(Suppl 54):18–23
75. Gordon KB, Langley RG, Leonardi C, Toth D, Menter MA, Kang S, Heffernan M, Miller B, Hamlin R, Lim L, Zhong J, Hoffman R, Okun MM (2006) Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: double-blind, randomized controlled trial and open-label extension study. *J Am Acad Dermatol* 55(4):598–606. doi:10.1016/j.jaad.2006.05.027
76. Gordon PM, Diffey BL, Matthews JNS, Farr PM (1999) A randomised comparison of narrow-band TL-01 phototherapy and PUVA photochemotherapy for psoriasis. *J Am Acad Dermatol* 41:728–732
77. Gottlieb A, Menter A, Mendelsohn A, Shen YK, Li S, Guzzo C, Fretzin S, Kunyetz R, Kavanaugh A (2009) Ustekinumab, a human interleukin 12/23 monoclonal antibody, for psoriatic arthritis: randomised, double-blind, placebo-controlled, cross-over trial. *Lancet* 373(9664):633–640. doi:10.1016/S0140-6736(09)60140-9
78. Gottlieb AB, Evans R, Li S, Dooley LT, Guzzo CA, Baker D, Bala M, Marano CW, Menter A (2004) Infliximab induction therapy for patients with severe plaque-type psoriasis: a randomized, double-blind, placebo-controlled trial. *J Am Acad Dermatol* 51(4):534–542. doi:10.1016/j.jaad.2004.02.021
79. Gottlieb AB, Ford RO, Spellman MC (2003) The efficacy and tolerability of clobetasol propionate foam 0.05% in the treatment of mild to moderate plaque-type psoriasis of nonscalp regions. *J Cutan Med Surg* 7(3):185–192. doi:10.1007/s10227-002-0114-5
80. Gottlieb AB, Matheson RT, Lowe N, Krueger GG, Kang S, Goffe BS, Gaspari AA, Ling M, Weinstein GD, Nayak A, Gordon KB, Zitnik R (2003) A randomized trial of etanercept as monotherapy for psoriasis. *Arch Dermatol* 139(12):1627–1632. doi:10.1001/archderm.139.12.1627 (discussion 1632)
81. Green L, Sadoff W (2002) A clinical evaluation of tazarotene 0.1% gel, with and without a high- or mid-high-potency corticosteroid, in patients with stable plaque psoriasis. *J Cutan Med Surg* 6(2):95–102. doi:10.1007/s10227-001-0031-z
82. Grossman RM, Thivolet J, Claudy A, Souteyrand P, Guilhaou JJ, Thomas P, Amblard P, Belaich S, de Belilovsky C, de la Brassinne M et al (1994) A novel therapeutic approach to psoriasis with combination calcipotriol ointment and very low-dose cyclosporine: results of a multicenter placebo-controlled study. *J Am Acad Dermatol* 31(1):68–74
83. Grundmann-Kollmann M, Ludwig R, Zollner TM, Ochsendorf F, Thaci D, Boehncke WH, Krutmann J, Kaufmann R, Podda M (2004) Narrowband UVB and cream psoralen–UVA combination therapy for plaque-type psoriasis. *J Am Acad Dermatol* 50(5):734–739. doi:10.1016/S0190
84. Guenther L, Van de Kerkhof PC, Snellman E, Kragballe K, Chu AC, Tegner E, Garcia-Diez A, Springborg J (2002) Efficacy and safety of a new combination of calcipotriol and betamethasone dipropionate (once or twice daily) compared to calcipotriol (twice daily) in the treatment of psoriasis vulgaris: a randomized, double-blind, vehicle-controlled clinical trial. *Br J Dermatol* 147(2):316–323
85. Guenther LC, Poulin YP, Pariser DM (2000) A comparison of tazarotene 0.1% gel once daily plus mometasone furoate 0.1% cream once daily versus calcipotriene 0.005% ointment twice daily in the treatment of plaque psoriasis. *Clin Ther* 22(10):1225–1238
86. Gupta AK, Goldfarb MT, Ellis CN, Voorhees JJ (1989) Side-effect profile of acitretin therapy in psoriasis. *J Am Acad Dermatol* 20(6):1088–1093
87. Hacker SM, Rasmussen JE (1992) The effect of flash lamp-pulsed dye laser on psoriasis. *Arch Dermatol* 128(6):853–855
88. Halevy S, Giryes H, Friger M, Sukenik H (1997) Dead sea bath salt for the treatment of psoriasis vulgaris: a double-blind controlled study. *J Eur Acad Dermatol Venereol* 9(3):237–242
89. Hanke CW, Steck WD, Roenigk HH Jr (1979) Combination therapy for psoriasis. Psoralens plus long-wave ultraviolet radiation with betamethasone valerate. *Arch Dermatol* 115(9):1074–1077
90. Harari M, Novack L, Barth J, David M, Friger M, Moses SW (2007) The percentage of patients achieving PASI 75 after 1 month and remission time after climatotherapy at the Dead Sea. *Int J Dermatol* 46(10):1087–1091. doi:10.1111/j.1365-4632.2007.03278.x
91. Hashizume H, Ito T, Yagi H, Takigawa M, Kageyama H, Furukawa F, Hata M, Shirahama S, Tanaka M, Higashishiba T, Machida H, Tsushima T, Matsushita K (2007) Efficacy and safety of preprandial versus postprandial administration of low-dose cyclosporin microemulsion (Neoral) in patients with psoriasis vulgaris. *J Dermatol* 34(7):430–434. doi:10.1111/j.1346-8138.2007.00305.x
92. Henseler T, Wolff K, Honigsman H, Christophers E (1981) Oral 8-methoxypsoralen photochemotherapy of psoriasis. The European PUVA study: a cooperative study among 18 European centres. *Lancet* 1(8225):853–857
93. Heydendael VM, Spuls PI, Opmeer BC, de Borgie CA, Reitsma JB, Goldschmidt WF, Bossuyt PM, Bos JD, de Rie MA (2003) Methotrexate versus cyclosporine in moderate-to-severe chronic plaque psoriasis. *N Engl J Med* 349(7):658–665. doi:10.1056/NEJMoa021359
94. Higgins E, Munro C, Marks J, Friedmann PS, Shuster S (1989) Relapse rates in moderately severe chronic psoriasis treated with cyclosporin A. *Br J Dermatol* 121(1):71–74
95. Housman TS, Keil KA, Mellen BG, McCarty MA, Fleischer AB Jr, Feldman SR (2003) The use of 0.25% zinc pyrithione spray does not enhance the efficacy of clobetasol propionate 0.05% foam in the treatment of psoriasis. *J Am Acad Dermatol* 49(1):79–82. doi:10.1067/mjd.2003.417
96. Housman TS, Pearce DJ, Feldman SR (2004) A maintenance protocol for psoriasis plaques cleared by the 308 nm excimer laser. *J Dermatolog Treat* 15(2):94–97. doi:10.1080/09546630310021947

97. Hroch M, Chladek J, Simkova M, Vaneckova J, Grim J, Martinkova J (2008) A pilot study of pharmacokinetically guided dosing of oral methotrexate in the initial phase of psoriasis treatment. *J Eur Acad Dermatol Venereol* 22(1):19–24. doi: [10.1111/j.1468-3083.2007.02264.x](https://doi.org/10.1111/j.1468-3083.2007.02264.x)
98. Hutchinson PE, Marks R, White J (2000) The efficacy, safety and tolerance of calcitriol 3 microg/g ointment in the treatment of plaque psoriasis: a comparison with short-contact dithranol. *Dermatology* 201(2):139–145
99. Ilknur T, Akarsu S, Aktan S, Ozkan S (2006) Comparison of the effects of pulsed dye laser, pulsed dye laser + salicylic acid, and clobetasole propionate + salicylic acid on psoriatic plaques. *Dermatol Surg* 32(1):49–55
100. Jarratt MT, Clark SD, Savin RC, Swinyer LJ, Safley CF, Brodell RT, Yu K (2006) Evaluation of the efficacy and safety of clobetasol propionate spray in the treatment of plaque-type psoriasis. *Cutis* 78(5):348–354
101. Kabat-Zinn J, Wheeler E, Light T, Skillings A, Scharf MJ, Cropley TG, Hosmer D, Bernhard JD (1998) Influence of a mindfulness meditation-based stress reduction intervention on rates of skin clearing in patients with moderate to severe psoriasis undergoing phototherapy (UVB) and photochemotherapy (PUVA). *Psychosom Med* 60(5):625–632
102. Katugampola GA, Rees AM, Lanigan SW (1995) Laser treatment of psoriasis. *Br J Dermatol* 133(6):909–913
103. Katz HI, Tanner DJ, Cuffie CA, Brody NI, Garcia CJ, Lowe NJ, Medansky RS, Roth HL, Shavin JS, Swinyer LJ (1998) A comparison of the efficacy and safety of the combination mometasone furoate 0.1%/salicylic acid 5% ointment with each of its components in psoriasis. *J Derm Treat* 9(3):151–156
104. Kaufmann R, Bibby AJ, Bissonnette R, Cambazard F, Chu AC, Decroix J, Douglas WS, Lowson D, Mascaro JM, Murphy GM, Stymne B (2002) A new calcipotriol/betamethasone dipropionate formulation (Daivobet) is an effective once-daily treatment for psoriasis vulgaris. *Dermatology* 205(4):389–393
105. Kaur J, Sharma VK, Sethuraman G, Tejasvi T (2008) Comparison of the efficacy of psoralen ultraviolet A with narrowband ultraviolet B phototherapy for the treatment of chronic plaque psoriasis with skin types IV and V. *Clin Exp Dermatol* 33(4):513–515. doi: [10.1111/j.1365-2230.2008.02718.x](https://doi.org/10.1111/j.1365-2230.2008.02718.x)
106. Kaur M, Oliver B, Hu J, Feldman SR (2006) Nonlaser UVB-targeted phototherapy treatment of psoriasis. *Cutis* 78(3):200–203
107. Khurshid K, Haroon TS, Hussain I, Pal SS, Jahangir M, Zaman T (2000) Psoralen-ultraviolet A therapy vs. psoralen-ultraviolet B therapy in the treatment of plaque-type psoriasis: our experience with Fitzpatrick skin type IV. *Int J Dermatol* 39(11):865–867
108. Kirby B, Buckley DA, Rogers S (1999) Large increments in psoralen-ultraviolet A (PUVA) therapy are unsuitable for fair-skinned individuals with psoriasis. *Br J Dermatol* 140(4):661–666
109. Kircik L, Bagel J, Korman N, Menter A, Elmets CA, Koo J, Yang YC, Chiou CF, Dann F, Stevens SR (2008) Utilization of narrow-band ultraviolet light B therapy and etanercept for the treatment of psoriasis (UNITE): efficacy, safety, and patient-reported outcomes. *J Drugs Dermatol* 7(3):245–253
110. Koc E, Tunca M, Akgul EO, Akar A, Kurt Y, Kurumlu Z, Erbil K, Kilic S (2009) Effects of etanercept on urine neopterin levels in patients with psoriasis in a controlled, open-label study. *J Dermatol* 36(4):191–196. doi: [10.1111/j.1346-8138.2009.00622.x](https://doi.org/10.1111/j.1346-8138.2009.00622.x)
111. Kolbach DN, Nieboer C (1992) Fumaric acid therapy in psoriasis: results and side effects of 2 years of treatment. *J Am Acad Dermatol* 27(5 Pt 1):769–771
112. Koo J, Blum RR, Lebwohl M (2006) A randomized, multicenter study of calcipotriene ointment and clobetasol propionate foam in the sequential treatment of localized plaque-type psoriasis: short- and long-term outcomes. *J Am Acad Dermatol* 55(4):637–641. doi: [10.1016/j.jaad.2006.05.026](https://doi.org/10.1016/j.jaad.2006.05.026)
113. Koo J, Cuffie CA, Tanner DJ, Bressinck R, Cornell RC, DeVillez RL, Edwards L, Breneman DL, Piacquadro DJ, Guzzo CA, Monroe EW (1998) Mometasone furoate 0.1%-salicylic acid 5% ointment versus mometasone furoate 0.1% ointment in the treatment of moderate-to-severe psoriasis: a multicenter study. *Clin Ther* 20(2):283–291
114. Koo JY, Lowe NJ, Lew-Kaya DA, Vasilopoulos AI, Lue JC, Sefton J, Gibson JR (2000) Tazarotene plus UVB phototherapy in the treatment of psoriasis. *J Am Acad Dermatol* 43(5 Pt 1):821–828. doi: [10.1067/mjd.2000.107940](https://doi.org/10.1067/mjd.2000.107940)
115. Koo JY, Martin D (2001) Investigator-masked comparison of tazarotene gel q.d. plus mometasone furoate cream q.d. vs. mometasone furoate cream b.i.d. in the treatment of plaque psoriasis. *Int J Dermatol* 40(3):210–212
116. Korver JE, Vissers WH, van Rens DW, Pasch MC, van Erp PE, Boezeman JB, van De Kerkhof PC (2007) A double-blind, randomized quantitative comparison of calcitriol ointment and calcipotriol ointment on epidermal cell populations, proliferation and differentiation. *Br J Dermatol* 156(1):130–137. doi: [10.1111/j.1365-2133.2006.07561.x](https://doi.org/10.1111/j.1365-2133.2006.07561.x)
117. Kragballe K, Jansen CT, Geiger JM, Bjerke JR, Falk ES, Gip L, Hjorth N, Lauharanta J, Mork NJ, Reunala T et al (1989) A double-blind comparison of acitretin and etretinate in the treatment of severe psoriasis. Results of a Nordic multicentre study. *Acta Derm Venereol* 69(1):35–40
118. Kragballe K, Noerrelund KL, Lui H, Ortonne JP, Wozel G, Uurasmaa T, Fleming C, Estebaranz JL, Hanssen LI, Persson LM (2004) Efficacy of once-daily treatment regimens with calcipotriol/betamethasone dipropionate ointment and calcipotriol ointment in psoriasis vulgaris. *Br J Dermatol* 150(6):1167–1173. doi: [10.1111/j.1365-2133.2004.05986.x](https://doi.org/10.1111/j.1365-2133.2004.05986.x)
119. Laburte C, Grossman R, Abi-Rached J, Abeywickrama KH, Dubertret L (1994) Efficacy and safety of oral cyclosporin A (CyA; Sandimmun) for long-term treatment of chronic severe plaque psoriasis. *Br J Dermatol* 130(3):366–375
120. Lago E, Carneiro S, Cuzzi T, Magalhaes G, Cassia F, Pessanha F, Ramos-e-Silva M (2007) Clinical and immunohistochemical assessment of the effect of cyclosporin in keratinocytes and dermal dendrocytes in psoriasis. *J Cutan Pathol* 34(1):15–21. doi: [10.1111/j.1600-0560.2006.00571.x](https://doi.org/10.1111/j.1600-0560.2006.00571.x)
121. Lebwohl M (2000) Strategies to optimize efficacy, duration of remission, and safety in the treatment of plaque psoriasis by using tazarotene in combination with a corticosteroid. *J Am Acad Dermatol* 43(2 Pt 3):S43–S46
122. Lebwohl M, Sherer D, Washenik K, Krueger GG, Menter A, Koo J, Feldman SR (2002) A randomized, double-blind, placebo-controlled study of clobetasol propionate 0.05% foam in the treatment of nonscalp psoriasis. *Int J Dermatol* 41(5):269–274
123. Lebwohl M, Yoles A, Lombardi K, Lou W (1998) Calcipotriene ointment and halobetasol ointment in the long-term treatment of psoriasis: effects on the duration of improvement. *J Am Acad Dermatol* 39(3):447–450
124. Lee CS, Koo J (2009) The efficacy of three class I topical synthetic corticosteroids, fluocinonide 0.1% cream, clobetasol 0.05% cream and halobetasol 0.05% cream: a Scholtz-Dumas bioassay comparison. *J Drugs Dermatol* 8(8):751–755
125. Leenutaphong V, Nimkulrat P, Suttim S (2000) Comparison of phototherapy two times and four times a week with low doses of narrow-band ultraviolet B in Asian patients with psoriasis. *Photodermatol Photoimmunol Photomed* 16(5):202–206

126. Lemme G, Campanati A, Paolinelli M, Offidani A (2007) Diffuse psoriasis plaque type and infliximab: our experience and review of literature. *G Ital Dermatol Venereol* 142:9–14
127. Leonardi CL, Kimball AB, Papp KA, Yeilding N, Guzzo C, Wang Y, Li S, Dooley LT, Gordon KB (2008) 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* 371(9625):1665–1674. doi:10.1016/S0140-6736(08)60725-4
128. Leonardi CL, Powers JL, Matheson RT, Goffe BS, Zitnik R, Wang A, Gottlieb AB (2003) Etanercept as monotherapy in patients with psoriasis. *N Engl J Med* 349(21):2014–2022. doi:10.1056/NEJMoa030409
129. Levell NJ, Shuster S, Munro CS, Friedmann PS (1995) Remission of ordinary psoriasis following a short clearance course of cyclosporin. *Acta Derm Venereol* 75(1):65–69
130. LeVine MJ, Parrish JA (1982) The effect of topical fluocinonide ointment on phototherapy of psoriasis. *J Invest Dermatol* 78(2):157–159
131. Liao YH, Chiu HC, Tseng YS, Tsai TF (2007) Comparison of cutaneous tolerance and efficacy of calcitriol 3 microg g(–1) ointment and tacrolimus 0.3 mg g(–1) ointment in chronic plaque psoriasis involving facial or genitofemoral areas: a double-blind, randomized controlled trial. *Br J Dermatol* 157(5):1005–1012. doi:10.1111/j.1365-2133.2007.08201.x
132. Litjens NH, Nibbering PH, Barrois AJ, Zomerdijk TP, Van Den Oudenrijn AC, Noz KC, Rademaker M, Van De Meide PH, Van Dissel JT, Thio B (2003) Beneficial effects of fumarate therapy in psoriasis vulgaris patients coincide with downregulation of type 1 cytokines. *Br J Dermatol* 148(3):444–451
133. Lotti T, Tripo L, Grazzini M, Krysenka A, Buggiani G, De Giorgi V (2009) Focused UV-B narrowband microphototherapy (Bioposorin). A new treatment for plaque psoriasis. *Dermatol Ther* 22(4):383–385. doi:10.1111/j.1529-8019.2009.01250.x
134. Lowe N, Feldman SR, Sherer D, Weiss J, Shavin JS, Lin YL, Foley V, Soto P (2005) Clobetasol propionate lotion, an efficient and safe alternative to clobetasol propionate emollient cream in subjects with moderate to severe plaque-type psoriasis. *J Dermatolog Treat* 16(3):158–164. doi:10.1080/09546630510041060
135. Magliocco MA, Pandya K, Dombrovskiy V, Christiansen L, Wong Y, Gottlieb AB (2006) A randomized, double-blind, vehicle-controlled, bilateral comparison trial of bexarotene gel 1% versus vehicle gel in combination with narrowband UVB phototherapy for moderate to severe psoriasis vulgaris. *J Am Acad Dermatol* 54(1):115–118. doi:10.1016/j.jaad.2005.09.012
136. Mahrle G, Schulze HJ (1990) The effect of initial external glucocorticoid administration on cignolin treatment of psoriasis. *Z Hautkr* 65(3):282, 285–287
137. Mahrle G, Schulze HJ, Farber L, Weidinger G, Steigleder GK (1995) Low-dose short-term cyclosporine versus etretinate in psoriasis: improvement of skin, nail, and joint involvement. *J Am Acad Dermatol* 32(1):78–88
138. Markham T, Rogers S, Collins P (2003) Narrowband UV-B (TL-01) phototherapy vs oral 8-methoxypsoralen psoralen-UV-A for the treatment of chronic plaque psoriasis. *Arch Dermatol* 139(3):325–328
139. Martin-Ezquerria G, Sanchez-Regana M, Umbert-Millet P (2007) Optimization of narrow-band uvb with a 5% oleic acid cream in the treatment of psoriasis. *J Drugs Dermatol* 6(3):290–292
140. Martin Ezquerria G, Sanchez Regana M, Herrera Acosta E, Umbert Millet P (2006) Topical tacrolimus for the treatment of psoriasis on the face, genitalia, intertriginous areas and corporal plaques. *J Drugs Dermatol* 5(4):334–336
141. McBride SR, Walker P, Reynolds NJ (2003) Optimizing the frequency of outpatient short-contact dithranol treatment used in combination with broadband ultraviolet B for psoriasis: a randomized, within-patient controlled trial. *Br J Dermatol* 149(6):1259–1265
142. Medansky RS, Cuffie CA, Tanner DJ (1997) Mometasone furoate 0.1%-salicylic acid 5% ointment twice daily versus fluocinonide 0.05% ointment twice daily in the management of patients with psoriasis. *Clin Ther* 19(4):701–709
143. Meffert H, Brautigam M, Farber L, Weidinger G (1997) Low-dose (1.25 mg/kg) cyclosporin A: treatment of psoriasis and investigation of the influence on lipid profile. *Acta Derm Venereol* 77(2):137–141
144. Menter A, Abramovits W, Colon LE, Johnson LA, Gottschalk RW (2009) Comparing clobetasol propionate 0.05% spray to calcipotriene 0.005% betamethasone dipropionate 0.064% ointment for the treatment of moderate to severe plaque psoriasis. *J Drugs Dermatol* 8(1):52–57
145. Menter A, Feldman SR, Weinstein GD, Papp K, Evans R, Guzzo C, Li S, Dooley LT, Arnold C, Gottlieb AB (2007) A randomized comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis. *J Am Acad Dermatol* 56(1):31 e31–e15. doi:10.1016/j.jaad.2006.07.017
146. Menter A, Tyring SK, Gordon K, Kimball AB, Leonardi CL, Langley RG, Strober BE, Kaul M, Gu Y, Okun M, Papp K (2008) Adalimumab therapy for moderate to severe psoriasis: a randomized, controlled phase III trial. *J Am Acad Dermatol* 58(1):106–115. doi:10.1016/j.jaad.2007.09.010
147. Mittal R, Malhotra S, Pandhi P, Kaur I, Dogra S (2009) Efficacy and safety of combination acitretin and pioglitazone therapy in patients with moderate to severe chronic plaque-type psoriasis: a randomized, double-blind, placebo-controlled clinical trial. *Arch Dermatol* 145(4):387–393. doi:10.1001/archdermatol.2009.5
148. Monastirli A, Georgiou S, Pasmatzis E, Sakkis T, Badavanis G, Drinas D, Sagriotis A, Tsambaos D (2002) Calcipotriol plus short-contact dithranol: a novel topical combination therapy for chronic plaque psoriasis. *Skin Pharmacol Appl Skin Physiol* 15(4):246–251
149. Moore A, Gordon KB, Kang S, Gottlieb A, Freundlich B, Xia HA, Stevens SR (2007) A randomized, open-label trial of continuous versus interrupted etanercept therapy in the treatment of psoriasis. *J Am Acad Dermatol* 56(4):598–603. doi:10.1016/j.jaad.2006.09.002
150. Morison WL, Momtaz K, Parrish JA, Fitzpatrick TB (1982) Combined methotrexate-PUVA therapy in the treatment of psoriasis. *J Am Acad Dermatol* 6(1):46–51
151. Mrowietz U, Christophers E, Altmeyer P (1998) Treatment of psoriasis with fumaric acid esters: results of a prospective multicentre study. German Multicentre Study. *Br J Dermatol* 138(3):456–460
152. Nast A, Boehncke WH, Mrowietz U, Ockenfels HM, Philipp S, Reich K, Rosenbach T, Sammain A, Schlaeger M, Sebastian M, Sterry W, Streit V, Augustin M, Erdmann R, Klaus J, Koza J, Muller S, Orzechowski HD, Rosumeck S, Schmid-Ott G, Weberschock T, Rzany B (2011) S3-guidelines for the treatment of psoriasis vulgaris. Update 2011. *J Dtsch Dermatol Ges* 9(Suppl 2):S1–S104. doi:10.1111/j.1610-0379.2011.07680.x
153. Nast A, Erdmann R, Pathirana D, Rzany B (2008) Translating psoriasis treatment guidelines into clinical practice—the need for educational interventions and strategies for broad dissemination. *J Eval Clin Pract* 14(5):803–806. doi:10.1111/j.1365-2753.2008.00971.x
154. Nast A, Kopp I, Augustin M, Banditt KB, Boehncke WH, Follmann M, Friedrich M, Huber M, Kahl C, Klaus J, Koza J, Kreiselmaier I, Mohr J, Mrowietz U, Ockenfels HM,

- Orzechowski HD, Prinz J, Reich K, Rosenbach T, Rosumeck S, Schlaeger M, Schmid-Ott G, Sebastian M, Streit V, Weberschock T, Rzany B (2007) German evidence-based guidelines for the treatment of psoriasis vulgaris (short version). *Arch Dermatol Res* 299(3):111–138. doi:10.1007/s00403-007-0744-y
155. Nast A, Kopp IB, Augustin M, Banditt KB, Boehncke WH, Follmann M, Friedrich M, Huber M, Kahl C, Klaus J, Koza J, Kreisellaier I, Mohr J, Mrowietz U, Ockenfels HM, Orzechowski HD, Prinz J, Reich K, Rosenbach T, Rosumeck S, Schlaeger M, Schmid-Ott G, Sebastian M, Streit V, Weberschock T, Rzany B (2006) S3-Guidelines for the therapy of psoriasis vulgaris. *J Dtsch Dermatol Ges* 4(Suppl 2):S1–S126. doi:10.1111/j.1610-0387.2006.06172.x
156. Nast A, Reytan N, Rosumeck S, Erdmann R, Rzany B (2008) Low prescription rate for systemic treatments in the management of severe psoriasis vulgaris and psoriatic arthritis in dermatological practices in Berlin and Brandenburg, Germany: results from a patient registry. *J Eur Acad Dermatol Venereol* 22(11):1337–1342. doi:10.1111/j.1468-3083.2008.02841.x
157. Nevitt GJ, Hutchinson PE (1996) Psoriasis in the community: prevalence, severity and patients' beliefs and attitudes towards the disease. *Br J Dermatol* 135(4):533–537
158. Nugteren-Huying WM, van der Schroeff JG, Hermans J, Suurmond D (1990) Fumaric acid therapy in psoriasis; a double-blind, placebo-controlled study. *Ned Tijdschr Geneesk* 134(49):2387–2391
159. Nyfors A, Brodthagen H (1970) Methotrexate for psoriasis in weekly oral doses without any adjunctive therapy. *Dermatologica* 140(6):345–355
160. Ohtsuka T (2008) The correlation between response to oral cyclosporin therapy and systemic inflammation, metabolic abnormality in patients with psoriasis. *Arch Dermatol Res* 300:545–550
161. Orfanos CE, Steigleder GK, Pullmann H, Bloch PH (1979) Oral retinoid and UVB radiation: a new, alternative treatment for psoriasis on an out-patient basis. *Acta Derm Venereol* 59(3):241–244
162. Ortonne JP, Kaufmann R, Lecha M, Goodfield M (2004) Efficacy of treatment with calcipotriol/betamethasone dipropionate followed by calcipotriol alone compared with tacalcitol for the treatment of psoriasis vulgaris: a randomised, double-blind trial. *Dermatology* 209(4):308–313. doi:10.1159/000080854
163. Ortonne JP, van de Kerkhof PC, Prinz JC, Bieber T, Lahfa M, Rubins A, Wozel G, Lorette G (2006) 0.3% tacrolimus gel and 0.5% tacrolimus cream show efficacy in mild to moderate plaque psoriasis: results of a randomized, open-label, observer-blinded study. *Acta Derm Venereol* 86(1):29–33. doi:10.1080/00015550510039817
164. Pacifico A, Daidone R, Peris K (2006) A new formulation of an occlusive dressing containing betamethasone valerate 0.1% in the treatment of mild to moderate psoriasis. *J Eur Acad Dermatol Venereol* 20(2):153–157. doi:10.1111/j.1468-3083.2006.01387.x
165. Papoutsaki M, Chimenti MS, Costanzo A, Talamonti M, Zangrilli A, Giunta A, Bianchi L, Chimenti S (2007) Adalimumab for severe psoriasis and psoriatic arthritis: an open-label study in 30 patients previously treated with other biologics. *J Am Acad Dermatol* 57(2):269–275. doi:10.1016/j.jaad.2006.12.003
166. Papp KA, Guenther L, Boyden B, Larsen FG, Harvima RJ, Guilhou JJ, Kaufmann R, Rogers S, van de Kerkhof PC, Hanssen LI, Tegner E, Burg G, Talbot D, Chu A (2003) Early onset of action and efficacy of a combination of calcipotriene and betamethasone dipropionate in the treatment of psoriasis. *J Am Acad Dermatol* 48(1):48–54. doi:10.1067/mjd.2003.130
167. Papp KA, Langley RG, Lebwohl M, Krueger GG, Szapary P, Yeilding N, Guzzo C, Hsu MC, Wang Y, Li S, Dooley LT, Reich K (2008) Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). *Lancet* 371(9625):1675–1684. doi:10.1016/S0140-6736(08)60726-6
168. Papp KA, Tying S, Lahfa M, Prinz J, Griffiths CE, Nakanishi AM, Zitnik R, van de Kerkhof PC, Melvin L (2005) A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. *Br J Dermatol* 152(6):1304–1312. doi:10.1111/j.1365-2133.2005.06688.x
169. Park YK, Kim HJ, Koh YJ (1988) Combination of photochemotherapy (PUVA) and ultraviolet B (UVB) in the treatment of psoriasis vulgaris. *J Dermatol* 15(1):68–71
170. Parker S, Coburn P, Lawrence C, Marks J, Shuster S (1984) A randomized double-blind comparison of PUVA-etretinate and PUVA-placebo in the treatment of chronic plaque psoriasis. *Br J Dermatol* 110(2):215–220
171. Parrish JA, Fitzpatrick TB, Tanenbaum L, Pathak MA (1974) Photochemotherapy of psoriasis with oral methoxsalen and longwave ultraviolet light. *N Engl J Med* 291(23):1207–1211
172. Paul BS, Momtaz K, Stern RS, Arndt KA, Parrish JA (1982) Combined methotrexate–ultraviolet B therapy in the treatment of psoriasis. *J Am Acad Dermatol* 7(6):758–762
173. Peharda V, Gruber F, Prpic L, Kastelan M, Brajac I (2000) Comparison of mometasone fluoroate 0.1% ointment and betamethasone dipropionate 0.05% ointment in the treatment of psoriasis vulgaris. *Acta Derm Venereol Croat* 8(4):223–226
174. Peroni A, Gisoni P, Zanoni M, Girolomoni G (2008) Balneotherapy for chronic plaque psoriasis at Comano spa in Trentino, Italy. *Dermatol Ther* 21(Suppl 1):S31–S38. doi:10.1111/j.1529-8019.2008.00200.x
175. Petrozzi JW (1983) Topical steroids and UV radiation in psoriasis. *Arch Dermatol* 119(3):207–210
176. Petzelbauer P, Honigsman H, Langer K, Anegg B, Strohal R, Tanew A, Wolff K (1990) Cyclosporin A in combination with photochemotherapy (PUVA) in the treatment of psoriasis. *Br J Dermatol* 123(5):641–647
177. Poulin YP (1999) Tazarotene 0.1% gel in combination with mometasone furoate cream in plaque psoriasis: a photographic tracking study. *Cutis* 63(1):41–48
178. Prins M, Swinkels OQ, Bouwhuis S, de Gast MJ, Bouwman-Boer Y, van der Valk PG, van de Kerkhof PC (2000) Dithranol in a cream preparation: disperse or dissolve? *Skin Pharmacol Appl Skin Physiol* 13(5):273–279
179. Prins M, Swinkels OQ, Van de Kerkhof PC, Van der Valk PG (2001) The impact of the frequency of short contact dithranol treatment. *Eur J Dermatol* 11(3):214–218
180. Radtke MA, Augustin M (2008) Economic considerations in psoriasis management. *Clin Dermatol* 26(5):424–431. doi:10.1016/j.clindermatol.2007.10.024
181. Ramsay CA, Schwartz BE, Lawson D, Papp K, Bolduc A, Gilbert M (2000) Calcipotriol cream combined with twice weekly broadband UVB phototherapy: a safe, effective and UVB-sparing antipsoriatic combination treatment. The Canadian Calcipotriol and UVB Study Group. *Dermatology* 200(1):17–24
182. Ranjan N, Sharma NL, Shanker V, Mahajan VK, Tegta GR (2007) Methotrexate versus hydroxycarbamide (hydroxyurea) as a weekly dose to treat moderate-to-severe chronic plaque psoriasis: a comparative study. *J Dermatolog Treat* 18(5):295–300. doi:10.1080/09546630701499291
183. Rapp SR, Feldman SR, Exum ML, Fleischer AB Jr, Reboussin DM (1999) Psoriasis causes as much disability as other major medical diseases. *J Am Acad Dermatol* 41(3 Pt 1):401–407

184. Reich K, Nestle FO, Papp K, Ortonne JP, Evans R, Guzzo C, Li S, Dooley LT, Griffiths CE (2005) Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. *Lancet* 366(9494):1367–1374. doi:[10.1016/S0140-6736\(05\)67566-6](https://doi.org/10.1016/S0140-6736(05)67566-6)
185. Reitamo S, Spuls P, Sassolas B, Lahfa M, Claudy A, Griffiths CE (2001) Efficacy of sirolimus (rapamycin) administered concomitantly with a subtherapeutic dose of cyclosporin in the treatment of severe psoriasis: a randomized controlled trial. *Br J Dermatol* 145(3):438–445
186. Revicki D, Willian MK, Saurat JH, Papp KA, Ortonne JP, Sexton C, Camez A (2008) Impact of adalimumab treatment on health-related quality of life and other patient-reported outcomes: results from a 16-week randomized controlled trial in patients with moderate to severe plaque psoriasis. *Br J Dermatol* 158(3):549–557. doi:[10.1111/j.1365-2133.2007.08236.x](https://doi.org/10.1111/j.1365-2133.2007.08236.x)
187. Richards HL, Fortune DG, Griffiths CE (2006) Adherence to treatment in patients with psoriasis. *J Eur Acad Dermatol Venereol* 20(4):370–379
188. Richards HL, Fortune DG, O’Sullivan TM, Main CJ, Griffiths CE (1999) Patients with psoriasis and their compliance with medication. *J Am Acad Dermatol* 41(4):581–583
189. Ring J, Kowalick L, Christophers E, Schill WB, Schopf E, Stander M, Wolff HH, Altmeyer P (2001) Calcitriol 3 microg g-1 ointment in combination with ultraviolet B phototherapy for the treatment of plaque psoriasis: results of a comparative study. *Br J Dermatol* 144(3):495–499
190. Robertson DB, McCarty JR, Jarratt M (1978) Treatment of psoriasis with 8-methoxypsoralen and sunlight. *South Med J* 71(11):1345–1349
191. Rogers S, Marks J, Shuster S, Briffa DV, Warin A, Greaves M (1979) Comparison of photochemotherapy and dithranol in the treatment of chronic plaque psoriasis. *Lancet* 1(8114):455–458
192. Rosina P, Giovannini A, Gisondi P, Girolomoni G (2009) Microcirculatory modifications of psoriatic lesions during topical therapy. *Skin Res Technol* 15(2):135–138. doi:[10.1111/j.1600-0846.2008.00336.x](https://doi.org/10.1111/j.1600-0846.2008.00336.x)
193. Salim A, Tan E, Ilchyshyn A, Berth-Jones J (2006) Folic acid supplementation during treatment of psoriasis with methotrexate: a randomized, double-blind, placebo-controlled trial. *Br J Dermatol* 154(6):1169–1174. doi:[10.1111/j.1365-2133.2006.07289.x](https://doi.org/10.1111/j.1365-2133.2006.07289.x)
194. Saraceno R, Andreassi L, Ayala F, Bongiorno MR, Giannetti A, Lisi P, Martini P, Peris K, Peserico A, Chimenti S (2007) Efficacy, safety and quality of life of calcipotriol/betamethasone dipropionate (Dovobet) versus calcipotriol (Daivonex) in the treatment of psoriasis vulgaris: a randomized, multicentre, clinical trial. *J Dermatolog Treat* 18(6):361–365. doi:[10.1080/09546630701646156](https://doi.org/10.1080/09546630701646156)
195. Saurat JH, Geiger JM, Amblard P, Beani JC, Boulanger A, Claudy A, Frenk E, Guilhou JJ, Grosshans E, Merot Y et al (1988) Randomized double-blind multicenter study comparing acitretin-PUVA, etretinate-PUVA and placebo-PUVA in the treatment of severe psoriasis. *Dermatologica* 177(4):218–224
196. Saurat JH, Stingl G, Dubertret L, Papp K, Langley RG, Ortonne JP, Unnebrink K, Kaul M, Camez A (2008) Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). *Br J Dermatol* 158(3):558–566. doi:[10.1111/j.1365-2133.2007.08315.x](https://doi.org/10.1111/j.1365-2133.2007.08315.x)
197. Schiener R, Brockow T, Franke A, Salzer B, Peter RU, Resch KL (2007) Bath PUVA and saltwater baths followed by UV-B phototherapy as treatments for psoriasis: a randomized controlled trial. *Arch Dermatol* 143(5):586–596. doi:[10.1001/archderm.143.5.586](https://doi.org/10.1001/archderm.143.5.586)
198. Schmid-Ott G, Malewski P, Kreiselmaier I, Mrowietz U (2005) Psychosocial consequences of psoriasis—an empirical study of disease burden in 3753 affected people. *Hautarzt* 56(5):466–472. doi:[10.1007/s00105-005-0906-9](https://doi.org/10.1007/s00105-005-0906-9)
199. Schopf RE, Aust H, Knop J (2002) Treatment of psoriasis with the chimeric monoclonal antibody against tumor necrosis factor alpha, infliximab. *J Am Acad Dermatol* 46(6):886–891
200. Serwin AB, Chodyncka B (2007) Soluble tumour necrosis factor-alpha receptor type 1 as a biomarker of response to phototherapy in patients with psoriasis. *Biomarkers* 12(6):599–607. doi:[10.1080/13547500701600597](https://doi.org/10.1080/13547500701600597)
201. Serwin AB, Wasowicz W, Chodyncka B (2006) Selenium supplementation, soluble tumor necrosis factor-alpha receptor type 1, and C-reactive protein during psoriasis therapy with narrowband ultraviolet B. *Nutrition* 22(9):860–864. doi:[10.1016/j.nut.2006.05.011](https://doi.org/10.1016/j.nut.2006.05.011)
202. Shupack JL, Jondreau L, Kenny C, Stiller MJ (1993) Diflorasone diacetate ointment 0.05% versus betamethasone dipropionate ointment 0.05% in moderate-severe plaque-type psoriasis. *Dermatology* 186(2):129–132
203. Smith CH, Jackson K, Bashir SJ, Perez A, Chew AL, Powell AM, Wain M, Barker JN (2006) Infliximab for severe, treatment-resistant psoriasis: a prospective, open-label study. *Br J Dermatol* 155(1):160–169. doi:[10.1111/j.1365-2133.2006.07316.x](https://doi.org/10.1111/j.1365-2133.2006.07316.x)
204. Snellman E, Klimenko T, Rantanen T (2004) Randomized half-side comparison of narrowband UVB and trimethylpsoralen bath plus UVA treatments for psoriasis. *Acta Derm Venereol* 84(2):132–137
205. Stein LF, Sherr A, Solodkina G, Gottlieb AB, Chaudhari U (2001) Betamethasone valerate foam for treatment of nonscalp psoriasis. *J Cutan Med Surg* 5(4):303–307. doi:[10.1007/s10227-001-0006-0](https://doi.org/10.1007/s10227-001-0006-0)
206. Stern RS, Nijsten T, Feldman SR, Margolis DJ, Rolstad T (2004) Psoriasis is common, carries a substantial burden even when not extensive, and is associated with widespread treatment dissatisfaction. *J Investig Dermatol Symp Proc* 9(2):136–139. doi:[10.1046/j.1087-0024.2003.09102.x](https://doi.org/10.1046/j.1087-0024.2003.09102.x)
207. Stinco G, Lautieri S, Valent F, Patrone P (2007) Cutaneous vascular alterations in psoriatic patients treated with cyclosporine. *Acta Derm Venereol* 87(2):152–154. doi:[10.2340/00015555-0216](https://doi.org/10.2340/00015555-0216)
208. Svensson AR, Gisslen H, Nordin P, Gios I (1992) A comparative study of mometasone furoate ointment and betamethasone valerate ointment in patients with psoriasis vulgaris. *Curr Ther Res Clin Exp* 52(3):390–396
209. Swinkels OQ, Prins M, Kucharekova M, de Boo T, Gerritsen MJ, van der Valk PG, van de Kerkhof PC (2002) Combining lesional short-contact dithranol therapy of psoriasis with a potent topical corticosteroid. *Br J Dermatol* 146(4):621–626
210. Tabolli S, Alessandrini L, Didona B, Di Pietro C, Gisondi P, Rota L, Sampogna F, Abeni D (2009) A randomized controlled trial to evaluate short-term treatment with eosin vs. topical steroids in psoriasis. *Clin Exp Dermatol* 34(3):304–308. doi:[10.1111/j.1365-2230.2008.02932.x](https://doi.org/10.1111/j.1365-2230.2008.02932.x)
211. Taibjee SM, Cheung ST, Laube S, Lanigan SW (2005) Controlled study of excimer and pulsed dye lasers in the treatment of psoriasis. *Br J Dermatol* 153(5):960–966. doi:[10.1111/j.1365-2133.2005.06827.x](https://doi.org/10.1111/j.1365-2133.2005.06827.x)
212. Tausk F, Whitmore SE (1999) A pilot study of hypnosis in the treatment of patients with psoriasis. *Psychother Psychosom* 68(4):221–225
213. Thaci D, Brautigam M, Kaufmann R, Weidinger G, Paul C, Christophers E (2002) Body-weight-independent dosing of cyclosporine micro-emulsion and three times weekly maintenance regimen in severe psoriasis. A randomised study. *Dermatology* 205(4):383–388

214. Thune P, Brolund L (1992) Short- and long-contact therapy using a new dithranol formulation in individually adjusted dosages in the management of psoriasis. *Acta Derm Venereol Suppl (Stockh)* 172:28–29
215. Torras H, Aliaga A, Lopez-Estebarez JL, Hernandez I, Gardeazabal J, Quintanilla E, Mascaro JM (2004) A combination therapy of calcipotriol cream and PUVA reduces the UVA dose and improves the response of psoriasis vulgaris. *J Dermatolog Treat* 15(2):98–103. doi:10.1080/09546630410023322
216. Traupe H, Robra BP (2002) Gesundheitsberichterstattung des Bundes, vol Heft 11. Robert-Koch-Institut, Berlin
217. Trehan M, Taylor CR (2002) Medium-dose 308-nm excimer laser for the treatment of psoriasis. *J Am Acad Dermatol* 47(5):701–708
218. Trott J, Gerber W, Hammes S, Ockenfels HM (2008) The effectiveness of PUVA treatment in severe psoriasis is significantly increased by additional UV 308-nm excimer laser sessions. *Eur J Dermatol* 18(1):55–60. doi:10.1684/ejd.2008.0311
219. Tyring S, Gottlieb A, Papp K, Gordon K, Leonardi C, Wang A, Lalla D, Woolley M, Jahreis A, Zitnik R, Cella D, Krishnan R (2006) Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. *Lancet* 367(9504):29–35. doi:10.1016/S0140-6736(05)67763-X
220. ul Bari A, Iftikhar N, ber Rahman S, Iftikhar N, ber Rahman S (2005) Comparison of PUVA and UVB therapy in moderate plaque psoriasis. *J Pak Assoc Dermatol* 15:26–31
221. Valbuena MC, Hernandez O, Rey M, Sanchez G, de Quintana LP (2007) Twice- vs. thrice-weekly MPD PUVA in psoriasis: a randomized-controlled efficacy study. *Photodermatol Photoimmunol Photomed* 23(4):126–129. doi:10.1111/j.1600-0781.2007.00294.x
222. van de Kerkhof PC, Cambazard F, Hutchinson PE, Haneke E, Wong E, Souteyrand P, Damstra RJ, Combemale P, Neumann MH, Chalmers RJ, Olsen L, Revuz J (1998) The effect of addition of calcipotriol ointment (50 micrograms/g) to acitretin therapy in psoriasis. *Br J Dermatol* 138(1):84–89
223. van de Kerkhof PC, Green C, Hamberg KJ, Hutchinson PE, Jensen JK, Kidson P, Kragballe K, Larsen FG, Munro CS, Tillman DM (2002) Safety and efficacy of combined high-dose treatment with calcipotriol ointment and solution in patients with psoriasis. *Dermatology* 204(3):214–221
224. van de Kerkhof PC, Segaeert S, Lahfa M, Luger TA, Karolyi Z, Kaszuba A, Leigh G, Camacho FM, Forsea D, Zang C, Boussuge MP, Paolozzi L, Wajdula J (2008) Once weekly administration of etanercept 50 mg is efficacious and well tolerated in patients with moderate-to-severe plaque psoriasis: a randomized controlled trial with open-label extension. *Br J Dermatol* 159(5):1177–1185. doi:10.1111/j.1365-2133.2008.08771.x
225. van de Kerkhof PC, van der Valk PG, Swinkels OQ, Kucharekova M, de Rie MA, de Vries HJ, Damstra R, Oranje AP, de Waard-van der Spek FB, van Neer P, Lijnen RL, Kunkeler AC, van Hees C, Haertlein NG, Hol CW (2006) A comparison of twice-daily calcipotriol ointment with once-daily short-contact dithranol cream therapy: a randomized controlled trial of supervised treatment of psoriasis vulgaris in a day-care setting. *Br J Dermatol* 155(4):800–807. doi:10.1111/j.1365-2133.2006.07393.x
226. van Lingen RG, de Jong EM, Berends MA, Seyger MM, van Erp PE, van de Kerkhof PC (2008) Good clinical response to anti-psoriatic treatment with adalimumab and methotrexate does not inflict a direct effect on compartmentalization of T-cell subsets: a pilot study. *J Dermatolog Treat* 19(5):284–287
227. van Lingen RG, Korver JE, van de Kerkhof PC, Berends MA, van Rens DW, Langewouters AM, Boezeman JB, Seyger MM, de Jong EM (2008) Relevance of compartmentalization of T-cell subsets for clinical improvement in psoriasis: effect of immune-targeted antipsoriatic therapies. *Br J Dermatol* 159(1):91–96. doi:10.1111/j.1365-2133.2008.08618.x
228. Vella Briffa D, Rogers S, Greaves MW, Marks J, Shuster S, Warin AP (1978) A randomized, controlled clinical trial comparing photochemotherapy with dithranol in the initial treatment of chronic plaque psoriasis. *Clin Exp Dermatol* 3(4):339–347
229. Vena GA, Cassano N, Agnusdei CP, Bellini M, Calabretta S, Centofani S, Cervadoro G, Coviello C, Curia S, Dattola S, de Caro C, del Brocco L, Donato L, Favero L, Ferrari A, Gianfaldoni R, Liguori G, Loconsole F, Lopreiato R, Malara G, Massimino SD, Nannipieri A, Pettinato M, Postiglione D, Postorioni C, Pronesti ME, Provenzano E, Puglisi Guerra A, Ricciuti F, Ruggiero G, Scudero A, Spitaleri S, Trinca Armati F, Valenti G, Vernaci R, Verrina F, Zagni GF, Zappala F (2005) Treatment of psoriasis vulgaris with calcipotriol betamethasone dipropionate combination followed by calcipotriol and assessment of the adjuvant basic use of urea-based emollients. *Eur J Inflamm* 3(1):37–41
230. Vena GA, Cassano N, Loconsole F, Malara G, Sciarrone C, Puglisi Guerra A (2006) Sequential treatment of psoriasis with infliximab followed by cyclosporin. Preliminary results of an open-label prospective study. *G Ital Dermatol Venereol* 141: 221–225
231. Vena GA, Galluccio A, De Simone C, Mastrandrea V, Buquichio R, La Greca S, Dattola S, Puglisi Guerra A, Donato L, Cantoresi F, De Pita O, Pezza M, M DA, Vernaci R, Miracapillo A, Valenti G, Cassano N (2009) A multicenter open-label experience on the response of psoriasis to Adalimumab and effect of dose escalation in non-responders: the Aphrodite project. *Int J Immunopathol Pharmacol* 22(1):227–233
232. Veraldi S, Caputo R, Pacifico A, Peris K, Soda R, Chimenti S (2006) Short contact therapy with tazarotene in psoriasis vulgaris. *Dermatology* 212(3):235–237. doi:10.1159/000091250
233. Vongthongsri R, Konschitzky R, Seeber A, Treitl C, Honigsmann H, Tanew A (2006) Randomized, double-blind comparison of 1 mg/L versus 5 mg/L methoxsalen bath-PUVA therapy for chronic plaque-type psoriasis. *J Am Acad Dermatol* 55(4):627–631. doi:10.1016/j.jaad.2006.05.024
234. Weinstein GD, Frost P (1971) Methotrexate for psoriasis. A new therapeutic schedule. *Arch Dermatol* 103(1):33–38
235. Weinstein GD, Koo JY, Krueger GG, Lebwohl MG, Lowe NJ, Menter MA, Lew-Kaya DA, Sefton J, Gibson JR, Walker PS (2003) Tazarotene cream in the treatment of psoriasis: two multicenter, double-blind, randomized, vehicle-controlled studies of the safety and efficacy of tazarotene creams 0.05% and 0.1% applied once daily for 12 weeks. *J Am Acad Dermatol* 48(5):760–767. doi:10.1067/mjd.2003.103
236. Weston WL, Fennessey PV, Morelli J, Schwab H, Mooney J, Samson C, Huff L, Harrison LM, Gotlin R (1988) Comparison of hypothalamus–pituitary–adrenal axis suppression from superpotent topical steroids by standard endocrine function testing and gas chromatographic mass spectrometry. *J Invest Dermatol* 90(4):532–535
237. White S, Vender R, Thaci D, Haverkamp C, Naeyaert J-M, Foster R, Martinez Escribano JA, Cambazard F, Bibby A (2006) Use of calcipotriene cream (Dovonex Cream) following acute treatment of psoriasis vulgaris with the calcipotriene/betamethasone dipropionate two-compound product (Taclonex). *Am J Clin Dermatol* 7(3):177–184
238. Yones SS, Palmer RA, Garibaldinos TT, Hawk JL (2006) Randomized double-blind trial of the treatment of chronic plaque psoriasis: efficacy of psoralen-UV-A therapy vs narrowband UV-B therapy. *Arch Dermatol* 142(7):836–842. doi:10.1001/archderm.142.7.836

239. Yoon HS, Youn JI (2007) A comparison of two cyclosporine dosage regimens for the treatment of severe psoriasis. *J Dermatolog Treat* 18(5):286–290. doi:[10.1080/09546630701418747](https://doi.org/10.1080/09546630701418747)
240. Youssef RM, Mahgoub D, Mashaly HM, El-Nabarawy E, Samir N, El-Mofty M (2008) Different narrowband UVB dosage regimens in dark skinned psoriatics: a preliminary study. *Photodermatol Photoimmunol Photomed* 24(5):256–259. doi:[10.1111/j.1600-0781.2008.00371.x](https://doi.org/10.1111/j.1600-0781.2008.00371.x)
241. Zachariae C, Mork NJ, Reunala T, Lorentzen H, Falk E, Karvonen SL, Johannesson A, Clareus B, Skov L, Mork G, Walker S, Qvitzau S (2008) The combination of etanercept and methotrexate increases the effectiveness of treatment in active psoriasis despite inadequate effect of methotrexate therapy. *Acta Derm Venereol* 88(5):495–501. doi:[10.2340/00015555-0511](https://doi.org/10.2340/00015555-0511)
242. Zaghoul SS, Goodfield MJ (2004) Objective assessment of compliance with psoriasis treatment. *Arch Dermatol* 140(4):408–414
243. Zhu X, Wang B, Zhao G, Gu J, Chen Z, Briantais P, Andres P (2007) An investigator-masked comparison of the efficacy and safety of twice daily applications of calcitriol 3 microg/g ointment vs. calcipotriol 50 microg/g ointment in subjects with mild to moderate chronic plaque-type psoriasis. *J Eur Acad Dermatol Venereol* 21(4):466–472. doi:[10.1111/j.1468-3083.2006.01913.x](https://doi.org/10.1111/j.1468-3083.2006.01913.x)

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