Actas Dermosifiliogr. 2010;**101(10)**:827–846

ACTAS
Dermo-Sifiliográficas

Full English text available at
www.elsevier.es/ad

CONSENSUS STATEMENT

Treatment of Scalp Psoriasis: Review of the Evidence and Delphi Consensus of the Psoriasis Group of the Spanish Academy of Dermatology and Venereology

L. Puig,[a,*] M. Ribera,[b] J.M. Hernanz,[c] I. Belinchón,[d] J. Santos-Juanes,[e] M. Linares,[f] I. Querol,[g] E. Colomé,[h] G. Caballé[i]

[a] *Servicio de Dermatología, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain*
[b] *Servicio de Dermatología, Hospital Universitari de Sabadell, Corporació Parc Taulí, Sabadell, Spain*
[c] *Servicio de Dermatología, Hospital Infanta Leonor, Madrid, Spain*
[d] *Servicio de Dermatología, Hospital General Universitario de Alicante, Alicante, Spain*
[e] *Servicio de Dermatología, Hospital Central de Asturias, Oviedo, Spain*
[f] *Servicio de Dermatología, Hospital Universitario Puerta del Mar, Cádiz, Spain*
[g] *Facultad de Medicina, Universidad de Zaragoza, Zaragoza, Spain*
[h] *Departamento Médico, LEO Pharma España, Barcelona, Spain*
[i] *Departamento de Ventas y Marketing, LEO Pharma España, Barcelona, Spain*

Manuscript received July 27, 2010; accepted for publication September 9, 2010

KEYWORDS
Psoriasis;
Scalp;
Treatment;
Process;
Delphi;
Topical corticosteroids;
Calcipotriol

Abstract
Scalp lesions are common in psoriasis and difficult to treat. Scientific evidence on the topic is scant and fragmentary, especially with respect to long-term treatment. This consensus statement is based on a critical assessment of the results of a MEDLINE search for clinical trials of the efficacy and safety of therapies used to treat scalp psoriasis. The recommendations were developed by an expert panel using the Delphi process to reach a consensus and then ratified by the members of the Psoriasis Group of the Spanish Academy of Dermatology and Venereology. The recommended induction therapy for scalp psoriasis is either a topical corticosteroid or a topical treatment combining calcipotriol and betamethasone. The choice of an appropriate vehicle is crucial in improving effectiveness and patient adherence to treatment. The only formulations that have been studied in the long-term treatment of scalp psoriasis are a combination of calcipotriol and betamethasone in gel and calcipotriol alone in solution.

*Corresponding author.
E-mail address: lpuig@santpau.cat (L. Puig).

0001-7310/$ - see front matter

PALABRAS CLAVE
Psoriasis;
Cuero cabelludo;
Tratamiento;
Consenso;
Delphi;
Corticoesteroides tópicos;
Calcipotriol

Tratamiento de la psoriasis del cuero cabelludo. Revisión de la evidencia y Consenso Delphi del Grupo de Psoriasis de la Academia Española de Dermatología y Venereología

Resumen
La afectación del cuero cabelludo resulta frecuente y de difícil tratamiento en los pacientes con psoriasis, siendo escasa y poco sistematizada la evidencia científica al respecto, en particular por lo que se refiere al tratamiento a largo plazo. En el presente documento de consenso, basado en una búsqueda (MEDLINE) de los ensayos clínicos publicados sobre la eficacia y seguridad de los diferentes tratamientos para la psoriasis del cuero cabelludo y su evaluación, se establecen unas recomendaciones, partiendo de un consenso Delphi por parte de un panel de expertos, refrendado por los miembros del Grupo de Psoriasis de la Academia Española de Dermatología y Venereología. El tratamiento de inducción recomendado para la psoriasis del cuero cabelludo son los corticoides tópicos y la combinación de calcipotriol/betametasona. La elección de un vehículo apropiado es decisiva para incrementar la eficacia y el cumplimiento del paciente. Únicamente la combinación de calcipotriol/betametasona en gel y el calcipotriol en solución se han estudiado en el tratamiento de la psoriasis del cuero cabelludo a largo plazo.

Introduction

The scalp is affected in 70% to 80% of patients with psoriasis.[1,2] Scalp lesions have specific characteristics that distinguish them from lesions on other parts of the body and make treatment more challenging. Hair makes topical treatments difficult to apply, and the proximity of the face limits the use of certain preparations because facial skin is more susceptible to adverse effects, such as iatrogenic rosacea, glaucoma, iatrogenic acne, and irritation.[3]

Moreover, many of the available topical therapies are rejected by patients because of their cosmetically unattractive effects. Almost half of patients with itchy and scaly psoriatic lesions on the scalp report having problems with social relationships as a result of their disease,[4] an indication that scalp involvement has a negative impact on the patients' health and quality of life because of the persistence and visibility of the lesions.[5]

The literature offers little evidence on the treatment of psoriasis of the scalp, and the treatment of scalp lesions is often based on studies of the response to the treatment of psoriasis on other areas of the body. Only very few controlled studies offering a high level of evidence (randomized double blind vehicle-controlled trials) have assessed pharmacologic treatments for psoriatic scalp lesions. This consensus statement reviews studies dealing specifically with the efficacy and safety of therapies used to treat psoriasis of the scalp and proposes recommendations drawn up by an expert panel using the Delphi process to reach a consensus, which was then ratified by the members of the Psoriasis Group of the Spanish Academy of Dermatology and Venereology.

Methods

Controlled trials and some observational studies dealing specifically with psoriasis affecting the scalp were selected for review. All were identified by a MEDLINE search (cut-off date, January 12, 2010) using the term "scalp psoriasis" followed by the different treatments and drugs used. The clinical trials were then evaluated according to the scale of the Scottish Intercollegiate Guidelines Network (SIGN).[6] Also reviewed were recently published guidelines[7] and review articles on the topical treatment of psoriasis of the scalp[8] as well as the Cochrane Collaboration review on the topical treatment of plaque psoriasis, which also deals with scalp involvement.[9] The recent European consensus on the treatment of psoriatic scalp lesions—also considered in the present review—presents a treatment algorithm that includes recommendations for patients with mild, moderate, or severe scalp lesions.[10]

This Spanish consensus statement was developed using the Delphi process.[11] The trials selected were appraised by a panel of 7 experts (the first 7 authors of this article), who indicated their degree of agreement with 57 statements on a Likert scale from 1 to 7. These questionnaire items were subsequently reassessed and redefined in a teleconference. Positive consensus was defined as assignment of a score of 6 or 7 by at least 70% of the expert appraisers. Negative consensus was defined as assignment of a score of 1 or 2 by at least 70% of the appraisers. The definitive list of items in the questionnaire the expert panel responded to was then submitted to 77 dermatologists throughout Spain, all members of the Psoriasis Group of the Spanish Academy of Dermatology and Venereology. This larger group also responded using the same Likert scale and the percentages were recorded.

Based on the available evidence, the expert panel then made a series of recommendations, which were rated according to the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) criteria.[12,13] These recommendations are described below and summarized in tables.

Severity, Quality of Life, and General Treatment Considerations

How the baseline severity of psoriasis is defined and how the effect of treatment is measured are crucial factors in assessing the response to treatment of psoriatic scalp lesions in clinical trials. The instruments used include the percentage of body surface area affected and the Psoriasis Area and Severity Index (PASI). The PASI has become the standard among the instruments used to measure the intensity of psoriasis.[14] It is used particularly in clinical trials, and a 75% reduction in PASI compared to baseline (PASI 75) is considered to be a standard measure of efficacy.[15] Validated and used as a measure of severity of psoriasis, PASI assessment separately considers the intensity of erythema, induration, and desquamation on 4 areas of the body, one of which is the head, an area that includes the face, neck, and scalp and accounts for 10% of the total body surface area. Another instrument used is the Psoriasis Scalp Severity Index (PSSI). This is also based on the degree of erythema, induration, and desquamation and the extent of the affected surface area, but only takes into account the scalp.[16]

A recent European consensus statement used a simple classification to define the severity of scalp lesions in its treatment algorithm[10] using the following categories: mild (involvement of <50% of the scalp and mild or minimal erythema, infiltration, and pruritus); moderate (involvement of >50% of the surface with moderate erythema, infiltration, and pruritus); and severe (involvement of >50% of the surface with moderate to severe erythema, infiltration, and pruritus and/or cicatricial alopecia or lesions on visible areas of the face). These categories are illustrated with photographs. In short, scaling, pruritus, and infiltration are minimal in cases of mild disease, moderate in moderate disease, and severe in severe cases, when they may be accompanied by evidence of hair loss.[10]

Scalp psoriasis, and especially moderate to severe disease, is associated with emotional and social consequences that affect the patient's overall health and wellbeing.[17] While psoriatic scalp lesions may last for many years—over 2 decades in 50% of patients[4]—and this highlights the importance of the psychological consequences, very few studies have evaluated the specific emotional repercussions of scalp involvement in this setting.

Health-related quality of life is usually measured with general questionnaires, such as the 36-Item Short Form Health Survey (SF-36)[18] or specific dermatology questionnaires, such as Skindex-29 and the Dermatology Life Quality Index, instruments that have been validated in Spain.[19] Scalpdex is a new 23-item tool that was recently developed to measure the quality of life of patients with psoriasis of the scalp.[20]

Topical treatment is the main therapeutic approach to scalp psoriasis, but the patients' attitude to such treatment, and in particular to the vehicle used, is different when the lesions are located on the scalp rather than on other parts of the body. The pharmaceutical formulation should be designed to prevent the easy spread of the preparation from the scalp to the face, and the patient must understand that the product should only be applied to the affected zone. Patients will not accept treatments that are unpleasant, difficult, or time consuming to apply; they demand easy-to-apply, fast-acting, and effective therapies. On the scalp, patients are reluctant to use creams and ointments, preferring lotions, gels, foams, and shampoos.

The many different types of treatment that have been used to treat scalp lesions include the classic tars and more refined coal tar derivatives, anthralin, keratolytic agents, vitamin A derivatives, phototherapy, corticosteroids, vitamin D analogs, and different combinations of topical products. Classic systemic treatments, such as methotrexate, ciclosporin, and the more recent biologic agents, can be prescribed for the more severe forms of the disease. This variety, particularly in the range of topical treatments available, reflects the generally poor patient adherence to treatment, which is probably due to patient dissatisfaction with many of the formulations either because of their low efficacy or the inconvenience and unpleasantness of their application.[21] The clinician must therefore focus not only on the efficacy of the treatment but also on finding a therapy with minimal local adverse effects that is cosmetically acceptable.

Table 1 shows the responses of the expert panel and the members of the Psoriasis Group of the Spanish Academy of Dermatology and Venereology on items for this section of the questionnaire.

Treatments for Psoriasis of the Scalp: Review of the Literature

Topical Corticosteroids

Corticosteroid creams have been the mainstay of treatment for psoriasis of the scalp for over 30 years, as the efficacy and rapid action of this family of topical treatments has made them one of the most frequently prescribed. Corticosteroids can be added to a number of different vehicles, for application as ointments, creams, emulsions, foams, gels, lotions, and shampoos. They can also be used in combination with other substances, such as salicylic acid, urea, coal tars, and vitamin D derivatives. Most randomized trials in the literature have studied formulations in shampoo or solution. No trials have been published on the foam products intended exclusively for scalp lesions, although novel alcohol-free foam products have been shown to be safe and effective in the treatment of psoriasis on other areas of the body.[22]

Efficacy

Betamethasone dipropionate or valerate, fluocinolone acetonide, mometasone furoate, and clobetasol propionate are some of the topical corticosteroids that have been most frequently studied in controlled clinical trials. Sixteen controlled trials of topical corticosteroids in the treatment of psoriasis of the scalp have been published (Table 2). In 5 trials studying a total of 807 patients these products were compared with a variety of vehicles and placebo.[23-27] The authors of a further 6 trials, including 1204 patients, compared 2 corticosteroids.[28-33] Finally, topical

Table 1 Positive Consensus on General Considerations Concerning the Treatment of Psoriasis of the Scalp

	Consensus of the Expert Panel				Consensus of the Psoriasis Group			
	Med	Pos	Neg	None	Med	Pos	Neg	None
General considerations								
Scalp lesions are more difficult to treat than lesions affecting other areas of the body.	7	85.7			7	81.2		
The area of the face adjacent to the scalp is more susceptible to irritation with certain formulations.	6	71.4			6			X
The emotional state of patients with psoriasis of the scalp can be affected by the disease.	6	85.7			6	85.7		
Quality of life is affected in patients with psoriatic scalp lesions.	6	71.4			6	83.1		
In my clinical practice I routinely use instruments to measure quality of life in patients who have psoriatic scalp lesions.	2			X	1			X
In psoriasis of the scalp, the vehicle used to apply topical treatment is of utmost importance.	7	100			7	88.3		
Gel is the preferred pharmaceutical formulation for use on the scalp.	6	71.4			6			X
Shampoo is the preferred pharmaceutical formulation for use on the scalp.	6	85.7			6			X
Foam is the preferred pharmaceutical formulation for use on the scalp.	6	71.4			6			X
Solution is the preferred pharmaceutical formulation for use on the scalp.	6	85.7			7	71.4		
Cream is the preferred pharmaceutical formulation for use on the scalp.	2		71		2		83.1	
Ointment is the preferred pharmaceutical formulation for use on the scalp.	1		100		1		87.0	
The treatment regimen depends on the intensity and extension of the lesions.	6	85.7			7	87.0		
Considerations relating to the pharmaceutical formulation that affect treatment compliance								
Cream formulations optimize adherence to treatment.	3			X	2		81.8	
Ointment formulations optimize adherence to treatment.	1		100		1		95.1	
Tar formulations optimize adherence to treatment.	2			X	1		83.1	
Gel formulations optimize adherence to treatment.	6	85.7			6			X
Shampoo formulations optimize adherence to treatment.	6	71.4			7	72.7		
Foam is the vehicle that optimizes adherence. to treatment	5			X	6			X
Oil is the vehicle that optimizes adherence to treatment.	3			X	4			X
Solution is the vehicle that optimizes adherence to treatment.	6	85.7			7	79.2		

Abbreviations: med, median; neg, negative consensus; pos, positive consensus.

corticosteroids were compared with a vitamin D analog, coal tar or a combination of betamethasone plus salicylic acid in 5 trials enrolling 936 patients.[28,34-37] Treatment efficacy was expressed as clearance or an excellent response reflected in the physician's global assessment or as a reduction in the total symptom score or global severity score.

In total, 807 patients with moderate to severe scalp psoriasis participated in 5 double blind placebo-controlled clinical trials of 2 to 4 weeks duration testing agents in a variety of vehicles (Table 2).[23-27]

Six trials compared different corticosteroids applied for 2 to 4 weeks in 1204 patients with moderate to severe

Table 2 Clinical Trials Evaluating the Efficacy of Topical Corticosteroids Compared to Other Treatments or Placebo

Reference	Study Design	Severity	Dose Regimens	Pharmaceutical Preparation	No. of Patients	Study Duration	% Response	Overall Efficacy	Evidence Level
Comparison with vehicle									
Lepaw[23]	db, r, cr	ND	Halcinonide 0.1 bid/plac	Solution	27	2 wks	59 vs 4[a]	>plac	1(−)
Olsen et al[24]	db, r	M/S	Clob 0.05 bid/plac	Solution	188/189	2 wks	69 vs 8.5[a]	>plac	1(+)
Pauporte et al[25]	db, r	M/S	Fluo 0.01% od vs plac	Oil	43/46	3 wks	83 vs 36[a]	>plac	1(+)
Jarrat et al[26]	db, r 2:1	M/S	Clob (0.05%)/ plac	Shampoo	95/47	4 wks	42 vs 2[b]	>plac	1(+)
Franz et al[27]	db, r 2:1	M/S	Bet Val bid (0.1%)/plac	Foam	57/28	4 wks	74 vs 10[a]	>plac	1(+)
				Solution	58/29		63 vs 6[a]	>plac >plac	
Comparison between corticosteroids									
Andreassi et al[28]	ib, r, cr	M/S	Bet Dip 0.05 bid	Shampoo	232	4 wks	88 vs 66[a]	Bet > standard	1(−)
			Other corticosteroids	Solution	128	2 wks			
Katz et al[29]	ib, r	M/S	Bet Dip 0.05 bid	Solution	96	3 wks	83 vs 75[c]	Bet > clob	1(+)
			Clob 0.05 bid	Solution	97	4 wks			
Brenemann et al[30]	op, r	M/S	Bet Dip 0.05 bid	Solution	83	3 wks	87 vs 84[c]	Bet≡fluo	1(+)
			Fluo (0.05%) bid	Solution	84	3 wks			
Feldman et al[31]	ib, r	M/S	Bet val bid	Foam	33		61 vs 52[c]	bid≡od	1(−)
			Bet Val od	Foam	46				
Vanderploeg et al[32]	ib, r	M/S	Mom 0.1% od	Solution	101		85 vs 70[c]	Mom > bet val	1(+)
			Bet val 0.1% bid	Solution	102				
Swinehart et al[33]	ib, r	M/S	Mom 0.1% od	Solution	103		78 vs 73[c]	Mom > bet val	1(+)
			Triam 0.1% bid	Solution	99				
Comparison with other drugs									
Reygagne et al[34]	ib, r	M/S	Clob 0.05% od	Shampoo	76	4 wks	50 vs 28[b]	Clob > vitD	1(++)
			Cal bid	Solution	75				
Klaber et al[35]	db, r	M/M	Bet val 0.1 bid	Solution	232	4 wks	75 vs 59[a]	Bet > vitD	1(++)
			Cal bid	Solution	236				
Andreassi et al[28]	ib, r, cr	M/S	Bet dip 0.05 od	Shampoo	232	4 wks	73 vs 46[c]	Bet > vitD	1(−)
			Cal	Solution	104				
Griffiths et al[36]	ib, r (3:1)	M/S	Clob 0.05% od	Shampoo	121	4 wks	50 vs 15[c]	Clob > tar	1(++)
			Tar 0.05 2/wk	Shampoo	41				
Hillström et al[37]	db, r		Bet dip 0.05 + salicylic acid 2% bid	Solution	51	3 wks	84 vs 60[d]	Bet sal > clob	1(−)
			Clob 0.05 bid	Solution					

Abbreviations: bid, twice daily; bet dip, betamethasone dipropionate; bet sal, betamethasone combined with salicylic acid; bet val, betamethasone valerate; cal, calcipotriol; clob, clobetasol; cr, crossover; db, double blind; fluo, fluocinolone; ib, investigator blinded; M/M, mild to moderate; M/S, moderate to severe; mom, mometasone; op, open; plac, placebo; r, randomized; triam, triamcinolone; vitD, vitamin D.

[a]Physician's global assessment: excellent response or cleared.

[b]Global severity score: clear or minimal disease.

[c]Reduction in total symptom score.

[d]Complete remission of signs and symptoms (pruritus).

psoriatic scalp lesions (Table 2).[28-33] Three of these trials evaluated the effect on the global severity score of the administration once or twice daily of betamethasone valerate in foam[31] or mometasone furoate in solution[32,33] compared to other corticosteroids. While in the first of those trials a reduction in symptoms was observed with twice daily administration of the drug, the study lacked the necessary statistical power to demonstrate differences between the 2 groups.[31] By contrast, once daily application of mometasone produced better results than twice daily applications of the comparison corticosteroid.[32,33]

In 5 randomized trials, a corticosteroid in shampoo or lotion was compared to a lotion combining a corticosteroid with salicylic acid, calcipotriol, or tar blend shampoo.[28,34-37] The corticosteroids produced better results than the comparators after 3 to 4 weeks of treatment. In a double blind trial in which 51 patients were assigned randomly to 0.05% clobetasol lotion or 2% betamethasone dipropionate with salicylic acid, the efficacy after 3 weeks was similar in both groups, although the combination yielded better results than clobetasol alone with respect to antipruritic effect.[37]

Safety

The safety of topical corticosteroid therapy depends both on the type of corticosteroid and the formulation used. The short contact time involved in the use of corticosteroid shampoos may minimize both local and systemic adverse effects. In a 4-week double blind trial enrolling 142 patients, 0.05% clobetasol propionate shampoo had the same safety profile as its vehicle, with the most frequently reported side effect being skin discomfort,[26] and patients do express preference for a corticosteroid over a tar-based product. Clobetasol shampoo (0.05%) has been shown to be better tolerated than calcipotriol solution.[34] Clobetasol has no systemic effects on either the hypothalamic-pituitary-adrenal axis or the eyes.[38] The effects on adrenal function have been assessed for up to 79 days. In a study that compared betamethasone dipropionate with a clobetasol propionate lotion (0.05%), no differences were found with respect to tolerability.[37] In another similar comparison, however, betamethasone was associated with a higher rate of folliculitis.[39]

Summary of the Review

Topical corticosteroids are a first-line option in the short term treatment of psoriasis of the scalp. Although high-potency corticosteroids are effective and reasonably safe, in general the recommended option is to use the lowest strength that will effectively clear the lesions since drug absorption is higher on the scalp. Compared to other topical treatments, corticosteroids are more effective than calcipotriol and coal tar, although there are very few comparative studies in the literature. Regarding long-term treatment (more than 4 weeks), there is insufficient evidence to support any conclusions concerning the efficacy and safety of corticosteroids in general or the advantages of one formulation over another.

Most studies with corticosteroids have been carried out using twice daily applications. Regimens requiring only one application daily using vehicles such as shampoo or lotion tend to favor adherence to treatment, in particular when the more potent preparations are being used. The application of a topical corticosteroid in the form of shampoo improves the quality of life and satisfaction of patients with psoriasis of the scalp.[40,41]

Topical corticosteroids should be applied with special care on the scalp because this highly vascularized area allows more of the active substance to enter into circulation. Moreover, when the lesions are located on the more sensitive facial skin adjacent to the scalp, there is a greater risk of skin atrophy and telangiectasia, especially in the case of long-term treatment. For all these reasons, corticosteroids work well in combination with vitamin D derivatives.

Table 3 summarizes the responses of the expert panel and the members of the Spanish Psoriasis Group (medians and percentages) for items related to this topic.

Recommendation of the Expert Panel

Based on published experience and the responses recorded, the use of topical corticosteroids in lotion or shampoo form is a first-line treatment for psoriasis of the scalp.

Grade of recommendation: A.

Vitamin D and Its Analogs

The vitamin D products and vitamin D analogs used in the treatment of scalp psoriasis are calcitriol, the dihydroxylated active form of vitamin D (1,25-dihydroxycholecalciferol), falecalcitriol, and the vitamin D analogs calcipotriol and tacalcitol. Vitamin D and its derivatives act by inhibiting the proliferation of keratinocytes, stimulating their differentiation, and inhibiting inflammation.[42]

Efficacy

The use of topical vitamin D analogs in the treatment of psoriatic scalp lesions has been studied in a number of controlled trials. There have also been several uncontrolled studies of large case series, which are not discussed in this article. A total of 1833 patients with mild to moderate psoriasis of the scalp have been included in clinical trials (322 in placebo-controlled trials). All of these trials used calcipotriol except for one in which the drug studied was tacalcitol. Most compared calcipotriol with a topical corticosteroid in monotherapy or in combination with salicylic acid, although it was also compared with coal tar products (Table 4).

In a 4-week double blind randomized clinical trial, calcipotriol solution was more effective than a placebo solution.[43] In the other randomized clinical trials, calcipotriol solution was compared to corticosteroids, coal tar shampoo, and a combination of betamethasone and salicylic acid.[34,35,44-48] Treatment efficacy was defined as clearance or an excellent response as per the physician's global assessment or as a reduction in the total symptom score or the global severity score after 4 to 12 weeks of treatment. When calcipotriol was compared to corticosteroids, the

Table 3 Positive or Negative Consensus on Treatment With Topical Corticosteroids

	Consensus of the Expert Panel				Consensus of the Psoriasis Group			
	Med	Pos	Neg	None	Med	Pos	Neg	None
General considerations								
Topical corticosteroids are the first-line therapy for short-term use.	6	71.4			7			X
Topical corticosteroids are the treatment for use when others have failed.	2			X	1		83.1	
Topical corticosteroids are the treatment best accepted by patients.	6	85.7			5			X
Topical corticosteroids are the most effective treatment for psoriasis of the scalp.	6	71.4			5			X
Which topical corticosteroid is the first-line treatment?								
Betamethasone dipropionate	6	85.7			5			X
Betamethasone valerate	5			X	5			X
Clobetasol propionate	6	71.4			5			X
Mometasone furoate	6			X	5			X

Abbreviations: med, median; neg, negative consensus; pos, positive consensus.

Table 4 Clinical Trials Evaluating the Therapeutic Efficacy of Vitamin D Analogs Compared to Other Treatments and Placebo

Reference	Study Design	Severity	Dose Regimen	Pharmaceutical Preparation	No. of Patients	Study Duration	% of Response	Overall Efficacy	Evidence Level
Comparison with Vehicle									
Green et al[43]	db, r, plac	M/M	Cal bid	Solution	25/24	4 wks	60 vs 17[a]	> plac	1(+)
Ruzicka et al[48]	db, r, plac	M/M	Tac qd	Emulsion	273	8 wks	53 vs 30[b]	> plac	1(++)
Comparison with other drugs									
Reygagne et al[34]	Ib, r	M/S	Cal bid	Solution	76	4 wks	50 vs 28[c]	VitD < clob	1(++)
			Clob (0.05%) qd	Shampoo	75				
Klaber et al[35]	db, r	M/M	Cal bid	Solution	236	4 wks	59 vs 75[a]	VitD < bet	1(++)
Klaber-McKinnon et al[44]		M/M/S	Bet val (0.1%) bid	Solution	232	8 wks	57 vs 37[d]		
Klaber-McKinnon et al[44] (follow-up)	op, r,	M/M/S	Cal bid	Solution	238	16 wks	Wk 24: –63%[b]	VitD > coal tar	1(++)
	op, nr		Capasal qd	Shampoo	237				
			Cal	Solution	166			Improvement	2(+)
Duweb et al[45]	op, r	ND	Cal bid	Solution	24	6 wks			
			Bet val (1%) bid	Solution	18		73 vs 72[d]	VitD≡bet	1(−)
Emaitig et al[46]	op, r	M/M/S	Cal bid	Solution	72	12 wks	97 vs 95[b]	VitD≡bet sal	1(−)
			Bet dip 0.05 + sal 2% bid	Solution					
Barret et al[47]	op, r	ND	Cal bid	Solution	ND	8 wks	56 vs 52	VitD≡vitD + tar	1(−)
			Cal + tar	Solution + shampoo					
Faergemann et al[74]	db, r	M/M	Itra + cal bid	Oral + solution	67	6 wks	70 vs 63[d]	Itra + vitD≡vitD	1(−)
			Plac + cal bid	Solution	70		Irritation 19 vs 47	Itra + vitD > vitD	

Abbreviations: bid, twice daily; bet, betamethasone; dip, dipropionate; val, valerate; cal, calcipotriol; clob, clobetasol; db, double blind; ib, investigator blinded; itra, itraconazole; M/M, mild to moderate; M/M/S, mild, moderate and severe; M/S, moderate to severe; op, open; plac, placebo; qd, once daily; r, randomized; sal, salicylic acid; tac, tacalcitol; vitD, vitamin D.

[a]Physician's global assessment: excellent response or cleared.

[b]Reduction in total symptom score.

[c]Global severity score: clear or minimal disease.

[d]Physician's global assessment.

latter produced significantly better results at 4 weeks. The effect of the calcipotriol solution increased after 8 to 12 weeks, when no differences were observed with respect to corticosteroids. It should be noted, however, that all of the trials lacked sufficient statistical power. The most interesting of the uncontrolled trials was one by Thaçi et al,[16] who assessed the efficacy and tolerability of calcipotriol solution applied during an 8-week period alone or in combination with other products in 3396 patients with mild to moderate psoriasis of the scalp. This treatment achieved a reduction in the PSSI from 18.4 to 5.6 ($P<.001$) and an improvement in the investigator's global assessment in 79.8% of patients.

In a randomized, double blind, multicenter trial, Ruzicka and Trompke[48] compared treatment with talcalcitol emulsion (4 μg/g) to placebo for 8 weeks in 273 patients with mild to moderate scalp psoriasis. They observed a greater reduction in the global severity score with tacalcitol than with placebo (58% and 30% respectively, $P<.001$). No trials have compared talcalcitol with other drugs used to treat scalp psoriasis.

Safety

The most common adverse event associated with calcipotriol solution is irritation, usually observed at the start of treatment. In an observational study of a calcipotriol solution in over 3000 patients, adverse events were recorded in only 2.4% of patients after 8 weeks of treatment.[16] In a 52-week observational study enrolling 202 patients, 18 adverse events were observed during the first 2 weeks, but after that the frequency of events gradually declined until only a single event occurred between weeks 28 and 52.[49] In the randomized controlled trials that compared calcipotriol to topical corticosteroids, more adverse events were associated with calcipotriol than with the corticosteroids. In a study by Klaber et al[37] in 474 patients, adverse events were reported for 87 patients in the calcipotriol group and 31 patients in the betamethasone group, leading to withdrawal of treatment in 4.6% and 0.9% of patients, respectively ($P=.017$).

It is possible that cutaneous irritation could be attenuated by the administration of oral itraconazole. One trial showed that application of calcipotriol by patients pretreated with itraconazole to reduce or eliminate colonies of *Malassezia furfur* was associated with less irritation than its application in a control group pretreated with placebo (19.4% versus 47.1%, $P>.001$).[50] The therapeutic effect on the scalp lesions was similar in both groups.

Summary of the Review

Vitamin D analogs are a safe and effective alternative for the treatment of psoriasis of the scalp. In 2 double blind comparative trials[34,35] calcipotriol was less effective than topical corticosteroids. In another 2 trials, neither of which had a sufficient sample size, no differences were observed between the treatment groups even though the treatments were administered for more than 4 weeks.[45,46] Long-term treatment with vitamin D derivatives, at least in psoriasis affecting other parts of the body, maintains its efficacy and is not associated with tachyphylaxis.[51] The most common adverse event is irritation, especially on the face. The adverse effects can be attenuated by reducing the frequency of application or by adding other treatments, such as topical corticosteroids. The frequency of adverse events also tends to decrease over time.

Table 5 summarizes the responses of the expert panel and the members of the psoriasis group.

Recommendation of the Expert Panel

Vitamin D analogs are second-line treatments in psoriasis of the scalp and have a good safety profile.

Grade of recommendation: B.

Combination Therapy With Vitamin D and Corticosteroids

Treatments combining 2 or more active ingredients are widely used in medicine because they can offer advantages over single-drug therapy, especially in terms of increased

Table 5 Positive or Negative Consensus on Treatment With Vitamin D Analogs

	Consensus of the Expert Panel				Consensus of the Psoriasis Group			
	Med	Pos	Neg	None	Med	Pos	Neg	None
General considerations								
Vitamin D analogs have an excellent safety profile.	6			X	6	74.0		
Which vitamin D Analog should be considered a first-line treatment.								
Calcitriol	3			X	3			X
Calcipotriol	4			X	5			X
Tacalcitol	2		71.4		3			X

Abbreviations: med, median; neg, negative consensus; pos, positive consensus.

efficacy and reductions in adverse events. The use of drugs that act in different ways on the same disease can result in a synergistic effect offering a good level of efficacy while also reducing the adverse effects of both drugs. Combination therapy is very common in the management of psoriasis. In the treatment of psoriatic scalp lesions, the combination of a topical corticosteroid and a topical vitamin D analog can reduce the irritation produced by the vitamin D and minimize the amount of topical corticosteroid required, thereby improving the safety profile of the treatment.[52] However, a certain chemical incompatibility exists when the combination involves 2 products that are stable at different pH levels, such as a vitamin D analog and a corticosteroid. There is evidence that this combination in the form of an ointment has an acceptable safety and efficacy profile and is well accepted by patients in the treatment of psoriasis.[53] However, an ointment is not an acceptable treatment for use on the scalp because it is greasy and difficult to apply and clean. Gel is the most appropriate vehicle for this drug combination in the treatment of psoriatic lesions on the scalp.

Efficacy

In initial open-label studies involving small samples and no comparator, an ointment containing calcipotriol and betamethasone improved symptoms and was associated with almost no adverse effects. [54-57]

To improve cosmetic acceptability, a new gel formulation of the calcipotriol/betamethasone combination for once daily application has been developed. Several randomized trials that compared this 2-compound product with each of its components in monotherapy have been published in recent years.[57-60] During the clinical development phase, the combination was studied in 4479 patients with mild, moderate, or severe scalp psoriasis, 313 in comparison with placebo and the rest in comparison with calcipotriol or betamethasone separately as monotherapy (Table 6).

In several 8-week controlled and double blind clinical trials, the combination of calcipotriol and betamethasone in gel applied once daily produced significantly better results than betamethasone dipropionate, calcipotriol, or its own vehicle when these were administered alone.[57-60] Treatment efficacy was defined as clearance or an excellent response as assessed by the investigator or as the proportion of patients who presented with "absent" or "very mild disease" in the global assessment of the investigator.

Another study evaluated the effect on quality of life of once daily application of the 2-compound gel (calcipotriol 50 µg/g plus betamethasone dipropionate 0.5 mg/g) compared to that of twice daily application of a calcipotriol solution (50 µg/mL); quality of life was measured using the SF-36 and the more specific Skindex-16 questionnaire.[61] Skindex-16 scores demonstrated a statistically significant difference in favor of the 2-compound therapy from week 2

Table 6 Clinical Trials Evaluating the Treatment Efficacy of Calcipotriol and Betamethasone in Gel Compared to Either Component Alone, Other Drugs, or Placebo

Reference	Study Design	Severity	Dose	Vehicle	No. of Patients	Study Duration	%Response	Overall Efficacy	Evidence Level
Compared to Placebo									
Tyring[60]	db, r, 3:1	ND	Cal/bet/plac	Gel	135/42	8 wks	72 vs 40[a]	Combi > plac	1(++)
Compared to other drugs									
Buckley[57]	db, r	M/M/S	Cal/bet qd	Gel	108	8 wks	83[a]	Combi > bet	1(++)
			Bet dip qd	Gel	110		74.6		1(++)
Jemec[58]	db, r	M/M/S	Cal/bet qd	Gel	541	8 wks	71,2[a]	Combi > bet	1(++)
	(1:1:2:4)		Bet dip qd	Gel	556		64	Combi > cal	
Van der	db, r	M/M/S	Cal qd	Gel	272		43.4	Combi > plac	
Kerkhof[59]	(1:1:2)		Plac	Gel	136		68.4[a]	Combi=bet	
Kragballe[62]	ib, r (2:1)	M/M/S	Cal/bet qd	Gel	568	8 wks	61	Combi > cal	
			Bet dip qd	Gel	563				
			Cal qd	Gel	286				
			Cal/bet qd	Gel	207	8 wks	69[a]	Combi > cal	1(++)
			Cal bid	Solution	105		31		
Luger[63]	db, r	M/M/S	Cal/bet qd	Gel	419	52 wks	60[a]	Combi > cal	1(++)
			Cal qd	Gel	431		47		

Abbreviations: bid, twice daily; bet, betamethasone; dip, dipropionate; cal, calcipotriol; combi, combination calcipotriol/betamethasone dipropionate; db, double blind; ib, investigator blinded; M/M/S, mild, moderate and severe; plac, placebo; qd, once daily; r, randomized.

[a]Physician's global assessment: excellent response or cleared.

onwards. The SF-36 results showed significant improvement from baseline in the group receiving the 2-compound gel formulation in both mental (weeks 2, 4, and 8, $P<.05$) and physical components (week 8, $P=.005$), while in the group treated with calcipotriol solution significant improvement was observed only in the mental component scores (week 8, $P=0.04$). In the same randomized, single blind study, fewer patients were symptomatic at week 8 in the group on the 2-compound gel than in the group on the vitamin D analog alone ((69% were symptom-free or had minimal disease in the former group versus 31% in the latter, $P<.001$).[62] The efficacy observed in the white patients has also been demonstrated in black and Hispanic patients with moderate to severe psoriasis of the scalp. Finally, in a randomized long-term (52-week) trial that compared the effect of a single daily application of a gel formulation containing calcipotriol (50 µg/g) plus betamethasone dipropionate (0.5 mg/g) to calcipotriol monotherapy in 869 patients with moderate to severe scalp psoriasis, Luger et al[63] found that the combination provided satisfactory control without prior application of keratolytic agents at 92.3% of the follow-up visits in the 2-compound group versus 80% in the calcipotriol group ($P<.001$).

Safety

The tolerability of these 2-compound formulations is similar to that of monotherapy with the corticosteroid, as the combination has been shown to attenuate the adverse effects associated with vitamin D monotherapy. In all the studies, the percentage of patients who reported a treatment-related adverse event was around 5% in both the 2-compound formulation group and the betamethasone group; in contrast, 13% in the group of patients who used calcipotriol and the placebo vehicle experienced adverse effects. Long-term use of the 2-compound formulation containing calcipotriol and betamethasone has been shown to be safe, with a 2.6% annual rate of adverse events possibly associated with treatment.[64]

Summary of the Review

Topical treatment combining a corticosteroid and a vitamin D analog (calcipotriol and betamethasone in gel) offers advantages over monotherapy with either of the components because it is more effective and minimizes the adverse effects. In 3 randomized trials, the 2-compound formulation was shown to be more effective than the topical corticosteroid alone and to have a similar or better safety profile in the treatment of exacerbations of scalp psoriasis (once daily application for 4 weeks). Once remission of the exacerbation has been achieved, intermittent regimens can be used (daily application 2 to 3 times a week) to control the disease. Topical corticosteroids are a first-line short term treatment of psoriasis of the scalp and, based on the available evidence, the 2-compound formulation with calcipotriol is more effective than monotherapy with either of the components and in many cases is an ideal treatment for mild, moderate or severe scalp involvement.

Table 7 summarizes the responses of the expert panel and the members of the psoriasis group.

Recommendation of the Expert Panel

The combination of corticosteroids and vitamin D analogs is more effective than single-drug therapy with either component and has fewer adverse effects than monotherapy with vitamin D. The 2-compound therapy combining a corticosteroid and a vitamin D analog is a first-line treatment for psoriasis of the scalp.

Grade of recommendation: A.

Other Topical Treatments

The older treatments for psoriasis of the scalp are currently less well accepted by patients, and their efficacy is based more on experience and expert opinion than on controlled clinical trials.

Table 7 Positive or Negative Consensus on Treatment With a Combination of Vitamin D and Topical Corticosteroid in Gel

	Consensus of the Expert Panel				Consensus of the Psoriasis Group			
	Med	Pos	Neg	None	Med	Pos	Neg	None
General considerations about vitamin D and topical corticosteroid combination in a gel								
This combination is the short-term first line treatment.	6	85.7			6			X
This combination is the most effective treatment for psoriasis of the scalp.	6	71.4			6			X
This combination treatment can improve efficacy and reduce adverse effects.	6	100			7	87.0		
Should this combination be considered a first-line treatment?								
Calcipotriol and betamethasone in gel.	7	100			6	71.4		

Abbreviations: med, median; neg, negative consensus; pos, positive consensus.

Efficacy

- Keratolytic agents
  The following agents have been used for their keratolytic properties: salicylic acid, alpha-hydroxy acids, and resorcinols. The penetration of other topical treatments appears to be enhanced by keratolytics, which usually eliminate hyperkeratotic scales and are, therefore, used prior to the application of other products. There are hardly any controlled trials of these products. The most widely used keratolytic agent is salicylic acid, which reduces desquamation by interacting with the desmosomes of the stratum corneum.[64] Salicylic acid, typically used at concentrations between 5% and 10%, is usually formulated in a solution, gel, ointment, or petroleum jelly. Some of these vehicles are rejected by patients as cosmetically unacceptable, which limits their use and reduces adherence to treatment. In an uncontrolled study that enrolled 30 patients with moderate to severe scalp psoriasis who applied a 6% salicylic acid gel, improvement was observed in most patients 3 to 6 weeks after start of treatment.[65] However, as this was an open-label study with a small sample and no comparison group, the conclusions should be interpreted with caution (evidence level 3).
- Dithranol and Tar Derivatives
  Coal tars have anti-inflammatory and antipruritic effects and inhibit epidermal proliferation. While their mechanism of action is poorly understood, they have been used for decades. Very few trials have been undertaken, but in an uncontrolled study of a coal-tar gel used by 112 patients, improvement was observed in 83% of patients, with remission persisting at 13 months in 30% of patients (evidence level 3).[66] In a randomized, investigator-blinded study, Griffiths et al[36] compared a 1% tar-blend shampoo (1%) with a 0.05% clobetasol propionate shampoo in 162 patients with moderate to severe scalp psoriasis. The corticosteroid shampoo was more effective than the tar product on all the scales evaluated (total and global severity score, $P<.001$) (see the section on topical corticosteroids).
  Dithranol (anthralin) has also been used effectively for decades in the treatment of psoriasis of the scalp. Although the mechanism of action remains unclear, it appears that anthralin induces the formation of free radicals directed against mitochondrial toxicity.[67] Wulff-Woesten et al[68] randomized 64 patients to receive dithranol in 1 of 3 formulations: an easily washed emulsifying oil base, a cream, or a combination of both cream and oil. Using a modified PASI assessment, they observed improvement in symptoms with the washable emulsifying oil base formulation after 1 and 2 weeks (34% and 57% reduction in PASI, respectively). By day 18, the psoriasis lesions had been reduced by 50% in the patients treated with the oil base formulation and by only 20% in those treated with the cream formulations ($P<.05$) (evidence level 1−).
- Topical Vitamin A Derivatives
  Tazarotene is an acetylenic retinoid available in 0.1% and 0.5% gel formulations. On contact with the skin it is converted into its active form, tazarotenic acid. No trials of this vitamin A derivative have been carried out specifically in scalp psoriasis, although in the opinion of some experts it could play a role in the therapeutic management of this condition.[69]
- Antifungal agents
  When psoriasis presents on the scalp in the form of scales, erythema, and pruritus, it is difficult to differentiate clinically or histologically between this entity and seborrheic dermatitis. Both entities have been associated with yeast infections caused by *Malassezia globosa, Malassezia restricta*, and *Malassezia furfur*. In fact, *Malassezia* yeasts are among the normal flora of human skin and, in the presence of certain predisposing factors, they can cause diseases such as pityriasis versicolor, *Malassezia* species folliculitis, seborrheic dermatitis, some forms of atrophic, reticulate papillomatosis, and systemic infections.[70] This pathogenic potential is the basis for the use of antifungal agents.[71] The following preparations have been used: 2% ketoconazole, 1.5% ciclopirox olamine, 2% clotrimazole and itraconazole (200 mg/d). Shemer et al[72] evaluated the efficacy of an ointment containing 40% urea and 1% bifonazole as the antifungal agent applied at night in 52 patients with psoriasis of the scalp and 17 patients with seborrheic dermatitis in an open-label trial. The ointment was applied once daily for 7 days (or 14 if no response was observed) and then once a week for 3 weeks. At the end of treatment, an improvement was observed in 24.6% of the patients with psoriasis of the scalp and 42.1% of the patients with seborrheic dermatitis (evidence level 2+). In a randomized placebo-controlled trial, Jury et al[73] studied the antifungal agent itraconazole (200 mg/d taken orally) in 28 patients with psoriasis of the scalp. After 2 weeks of treatment, no differences in PASI scores were observed between the group taking the oral antifungal agent and the controls. Sample size, study duration, and the use of oral treatment may all have contributed to the lack of any appreciable difference between the groups (evidence level 1−).

The question of whether pretreatment with an antifungal agent could reduce the local irritation caused by calcipotriol has also been studied. More abundant colonization with *Malassezia* yeasts has been observed in the areas where irritation occurred following treatment with calcipotriol solution. Starting from the hypothesis that *Malassezia* yeast species could interfere with topical calcipotriol therapy, Faergermann et al[74] undertook an 8-week double blind clinical trial in which 137 patients with psoriatic scalp lesions were randomized to pretreatment with either itraconazole or placebo. After 2 weeks of pretreatment, calcipotriol solution was applied daily for 6 weeks in both groups. The percentage of patients who presented local irritation was lower in the group treated with itraconazole than in the control group (19.4% and 47.1% respectively, $P<.001$). Skin irritation caused by calcipotriol was also less evident in the patients with lower-grade *Malassezia* yeast colonization ($P=.017$) (evidence level 1++).

Safety

No large controlled trials have been carried out with dithranol because of the reddish brown stains it leaves and the irritation it causes in some patients. Moreover, all the formulations of dithranol are difficult to wash off the scalp, which limits its use to specialized dermatology clinics and selected patients.

For some time, the safety of tars and their derivatives has been questioned because of their mutagenic potential[75] and because their use has been associated with nonmelanoma skin cancers.[76] The disagreeable smell and staining associated with the use of tar are other factors that have relegated these treatments to a minor role. New tar formulations that do not discolor the skin are currently being investigated.[77] Tazarotene has not been used on the scalp, but it can irritate the skin, causing associated adverse effects such as erythema, a burning sensation, and pruritus.[78]

Summary of the Review

The use of the topical treatments discussed in this section is based on many decades of clinical experience, but there is a paucity of rigorously designed controlled trials. Furthermore, the use of this very heterogeneous group of compounds is limited by their adverse effects. Owing to its unfavorable cosmetic characteristics and weak effect compared to topical corticosteroids, coal tar is being displaced by other therapies. Anthralin causes skin irritation. While there is broad clinical experience with tazarotene, no controlled trials have specifically studied its application in scalp psoriasis, although it is considered more effective than its vehicle in cream or gel formulations.[79] Owing to its potent keratolytic action, salicylic acid enhances the action of certain topical corticosteroids.

Table 8 summarizes the responses of the expert panel and the members of the psoriasis group on this section of the questionnaire.

Recommendation of the Expert Panel

The topical therapies other than the corticosteroids and vitamin D derivatives can be used when first-line treatments are contraindicated or fail to produce any response.

Grade of recommendation: C-D.

Physical therapy

Phototherapy and Grenz Ray Therapy

Efficacy

Phototherapy is a classic treatment for psoriasis, although few studies have been carried out. Both psoralen plus UV-A (PUVA) and narrow-band UV-B (311 nm) phototherapies have been used. However, the application of UV radiation on the scalp is difficult because hair blocks the penetration of the rays. Combs that emit UV-B radiation (308 nm) have recently been designed for use on thick hair. Used in conjunction with a scalp heater, they achieve better penetration.[80] The very few controlled trials carried out specifically on psoriasis affecting the scalp all have low statistical power. When phototherapy was compared with the application of betamethasone valerate lotion in 44 patients, no differences were observed between the 2 treatments although in the post-treatment follow-up the percentage of recurrence was lower in the group treated with phototherapy.[81] No trials have compared Grenz rays with placebo. Grenz rays emit electromagnetic radiation that penetrates more superficially than normal x-rays. The

Table 8 Positive or Negative Consensus on Topical Treatments Other than Vitamin D Derivatives and Corticosteroids

	Consensus of the Expert Panel				Consensus of the Psoriasis Group			
	Med	Pos	Neg	None	Med	Pos	Neg	None
General considerations								
Products derived from tar and coal tar are the treatments best accepted by patients.	2	85.7			1		80.5	
Vitamin A derivatives are the first-line treatment for psoriasis of the scalp.	2	71.4			2			X
Vitamin A derivatives are the most effective treatment for psoriasis of the scalp.	2	71.4			2		71.4	
Which of the following should be considered first-line treatments?								
Dithranol	2		71.4		2			X
Salicylate in petrolatum	2		71.4		3			X
Coal tar	2		71.4		2			X
Tazarotene	2		85.7		2			X
Antifungal agents	3			X	2		80.5	
Phototherapy	3			X	2		81.8	

Abbreviations: med, median; neg, negative consensus; pos, positive consensus.

combination of Grenz rays with corticosteroids has been shown to offer only marginal benefits in psoriasis of the scalp.[82]

Safety

The treatment of the scalp with UV-B radiation (308 nm) produces erythematic lesions and intense heat in all patients.

Summary of the Review

Phototherapy is difficult to use on the scalp and should be considered a second-line treatment.

Recommendation of the Expert Panel

There is insufficient evidence to support a recommendation.

Systemic Therapies

Systemic therapies are limited to patients with scalp psoriasis that has not responded to topical treatment and to patients with lesions in other areas of the body that have failed to respond to less aggressive therapies. Systemic therapies may be conventional ones (methotrexate, ciclosporin, acitretin, and fumaric acid esters) or biologic agents (etanercept, infliximab, adalimumab, alefacept, and ustekinumab). While there is a paucity of studies with a high level of scientific evidence dealing specifically with the topical treatment of scalp lesions, there are simply no trials in the literature specifically designed to evaluate the effect of systemic therapies on scalp psoriasis. However, clinical experience suggests that when a patient's psoriasis responds to systemic treatment, scalp lesions improve at least as much as those in other areas and such treatment sometimes achieves complete clearance of the scalp.[83]

Efficacy

- Classic Systemic Therapies
  Methotrexate has traditionally been used to treat moderate to severe cases of psoriasis that respond poorly or not at all to topical treatment. Methotrexate is a folic acid analog that reduces DNA and RNA synthesis by inhibiting purine synthesis. In patients with conventional psoriasis, there is evidence that methotrexate is effective because of its anti-inflammatory and antiproliferative properties.[2] In a study with evidence level A, methotrexate produced a remission in 40% of patients (>90% reduction in PASI).[84] Comparative trials have shown methotrexate to be less effective than either ciclosporin or adalimumab.[85,86] No studies have specifically evaluated methotrexate in scalp psoriasis.
  Ciclosporin, a cyclic peptide composed of 11 amino acids, is isolated from the spores of the fungus *Tolypocladium inflatum Gams*. It has been widely used as an immunosuppressant to prevent the rejection of organ transplants, and its mechanism of action in plaque psoriasis remains unclear. In several trials that have evaluated systemic treatment of psoriasis with ciclosporin alone, PASI 75 response rates have been observed in 50% to 70% of patients, depending on the dose used.[87,88]
  The systemic retinoid acitretin, an active metabolite of etretinate that inhibits keratinocyte proliferation, is used in cases of severe psoriasis that have failed to respond to topical treatment. The use of acitretin in the treatment of severe psoriasis has been studied[89] but not its specific use in the treatment of scalp lesions. Positive results are usually observed only after 24 weeks of treatment.[90]
  The use of fumaric acid esters, which act by interacting with glutathione, has been evaluated in 2 studies, neither of which dealt with psoriasis of the scalp.[91,92]

Biologic Systemic Therapies

Adalimumab, a recombinant humanized monoclonal antibody, is an immunoglobulin-G that inhibits tumor necrosis factor alpha (TNF-α) and reduces the expression of other inflammation markers. Its efficacy in moderate to severe plaque psoriasis has been demonstrated in 2 placebo-controlled randomized trials,[93,94] but the results relating to scalp psoriasis have only been presented in the form of a poster. In the BELIEVE study, the scalp was affected in 90% of the patients and the active treatment reduced the PSSI from 17.9 at baseline (n = 663) to 3.5 at week 8 (n = 640).[95] Etanercept, a fusion protein that includes the soluble TNF-α receptor and neutralizes this cytokine, has been evaluated in a number of randomized trials involving patients with moderate to severe plaque psoriasis.[96-99] In a 54-week open study, 711 patients with scalp psoriasis were randomized to either a continuous or an intermittent treatment regimen. Severity as measured by the PSSI improved significantly from a mean baseline score of 2.78 in both regimens, although the improvement was greater in the patients receiving continuous treatment (final follow-up PSSI, 0.89) than in those treated intermittently (final follow-up PSSI, 1.28).[100]

Infliximab is a monoclonal antibody against TNF-α with proven efficacy in psoriasis.[101,102] However, its use in the treatment of psoriatic plaques on the scalp has not been specifically evaluated.

Alefacept is a recombinant human fusion protein with immunoglobulin-G that inhibits the activation of T-cells by binding to the CD2 receptor. Alefacept has been shown to be effective in certain subgroups of psoriatic patients.[103,104] In a 16-week open trial, alefacept therapy (15 mg/wk by intramuscular injection) was evaluated in 30 patients with psoriatic plaques on the scalp.[105] Response was measured by evaluating the percentage of patients with a "clear" or "almost clear" assessment, a result reported in 16.7% of cases at the 6-week follow-up. Alefacept is not available in Spain.

Ustekinumab is a human monoclonal antibody that binds to the p40 protein subunit of interleukins 12 and 23. In 2 studies involving over 2000 patients with psoriasis, at week 12 improvement was observed in the PASI of at least 75%

in 66% to 76% of patients with ustekinumab and in only 3% to 5% of patients receiving placebo.[106,107] The improvement was observed throughout the follow-up period (52-76 weeks). Psoriasis of the scalp was not specifically studied.

Safety

The limitations affecting the use of methotrexate are related to its many adverse effects, which include hematopoietic suppression, liver abnormalities, gastrointestinal symptoms, and in some cases hair loss. The chief adverse events associated with ciclosporin are hypertension and increased serum creatinine, making continuous monitoring of renal function essential; this drug is also associated with an increase in the development of nonmelanoma skin cancer. Oral retinoids have mucocutaneous and musculoskeletal adverse effects, in particular cheilitis and dryness of the skin and mucosal surfaces. The high teratogenicity of acitretin makes strict contraceptive measures necessary during treatment and for years after its completion. Retinoids also alter liver function and the lipid profile. The safety profile of fumaric acid esters is characterized by the frequent development of gastrointestinal disorders and flushing. The adverse events most often reported for adalimumab are upper respiratory tract infections and local reactions at the injection site. However, severe psoriasis of the scalp with diffuse alopecia induced during adalimumab treatment has recently been reported.[108] In the PHOENIX 1 and 2 studies, ustekinumab was associated with a rate of adverse events similar to that of placebo.[106,107] However, the long-term safety profile of this drug with respect to infections and neoplasms is not yet completely clear.[109]

Table 9 summarizes the responses of the expert panel and the members of the psoriasis group with regard to systemic treatments.

Recommendation of the Expert Panel

Systemic treatments are used to treat very severe psoriasis of the scalp or patients with moderate to severe psoriasis in other sites that requires systemic treatment (Table 9).

Grade of recommendation: D.

Conclusion

The main recommendations concerning the treatment of psoriasis of the scalp obtained from the Delphi process are shown below and in Tables 10-12.

1. In the topical treatment of psoriasis of the scalp, the vehicle is of the utmost importance. Lotions, shampoos, and gels are associated with the best rates of adherence and are the preparations preferred by dermatologists.
2. Although the patient's emotional well-being and quality of life can be affected by the presence of psoriatic scalp lesions, dermatologists rarely make use of instruments that analyze these aspects.
3. Potent topical corticosteroids are the first-line treatment for acute flares of psoriasis on the scalp.
4. Vitamin D analogs are a second-line treatment with a very good safety profile.
5. Two-compound formulations that combine calcipotriol and betamethasone in gel are, together with topical corticosteroids, the most effective first-line treatments for psoriatic scalp lesions.
6. Systemic agents are an alternative for use when other treatments have failed and should not be considered first-line treatments for scalp psoriasis.
7. Treatment of scalp psoriasis requires a 2-phase regimen: induction therapy until improvement or remission is achieved followed by maintenance treatment.

Table 9 Positive or Negative Consensus on Systemic Treatments

	Consensus of the Expert Panel				Consensus of the Psoriasis Group			
	Med	Pos	Neg	None	Med	Pos	Neg	None
General considerations								
Systemic treatments should be used when other options have failed.	6	71.4			6			X
Systemic treatments have the best safety profile.	2		71.4		2			X
Which systemic drug should be considered a first-line treatment?								
Methotrexate	3			X	2		72.7	
Ciclosporin	2			X	2			X
Acitretin	2		70.1		2			X
Fumaric acid esters	2		85.7		1		87.0	
Adalimumab	2		71.4		1		81.8	
Etanercept	2		71.4		1		80.5	
Infliximab	2		71.4		1		87.0	
Ustekinumab	2		85.7		1		79.2	

Abbreviations: med, median; neg, negative consensus; pos, positive consensus.

Table 10 Treatment Regimens for Psoriasis of the Scalp

	Consensus of the Expert Panel				Consensus of the Psoriasis Group			
	Med	Pos	Neg	None	Med	Pos	Neg	None
General considerations								
A 2-phase regimen is required (induction until improvement or remission is achieved, followed by maintenance treatment).	6	85.7			6			X
Preferred induction treatments								
Antifungal shampoo	2		71.4		2		70.1	
Corticosteroids in solution	6	71.4			6			X
Combination of vitamin D + corticosteroids	7	100			7	76.6		
Usual duration of induction therapy								
Less than 1 week	2			X	2		79.2	
From 2 to 3 weeks	6			X	6	85.7		
Case by case basis	3			X	7	71.4		
Usual frequency of induction treatment								
1 application daily	6	71.4			7			X
Weekly (1-2 days a week)	2		71.4		1		81.8	

Abbreviations: med, median; neg, negative consensus; pos, positive consensus.

Table 11 There is Evidence Supporting a 2-Phase Regimen in the Following Treatments

	Consensus of the Expert Panel				Consensus of the Psoriasis Group			
	Med	Pos	Neg	None	Med	Pos	Neg	None
Antifungal shampoo	2		85.7		2			X
Tar-based shampoo	2		100		4			X
Keratolytic agents	2		100		4			X
Combination of vitamin D + corticosteroids	6	100			7	71,4		

Abbreviations: med, median; neg, negative consensus; pos, positive consensus.

Table 12 Treatment Regimens During the Maintenance Phase in Psoriasis of the Scalp

	Consensus of the Expert Panel				Consensus of the Psoriasis Group			
	Med	Pos	Neg	None	Med	Pos	Neg	None
Preferred treatments during the maintenance phase								
Combination of vitamin D + corticosteroids	6				6			
Vitamin D analogs	6				6			
Usual duration of treatment during the maintenance phase								
Less than 1 week	1		71.4		2		80.5	
Case by case depending on response	6	85.7			7			X
The usual frequency of maintenance treatment								
Two applications daily	3			X	1		76.6	
Weekly (1-2 days a week)	7	71.4			6	71.4		

Abbreviations: med, median; neg, negative consensus; pos, positive consensus.

8. The preferred treatments for the induction phase are corticosteroid solutions and combination formulations containing calcipotriol and betamethasone administered once daily for 3 weeks.
9. The preferred maintenance treatments are vitamin D analogs and combination formulations containing calcipotriol and betamethasone.
10. The fixed-dose combination of betamethasone and calcipotriol produces better results in terms of efficacy and safety during the induction phase than monotherapy with either of the 2 components and also reduces the quantity of corticosteroid required.
11. Maintenance therapy with the fixed dose combination of betamethasone and calcipotriol is as safe as vitamin D analogs and more effective.

The GRADE recommendations of the expert panel on the topical treatment of psoriasis of the scalp during

Table 13 GRADE Recommendations of the Expert Panel for the Topical Treatment of Psoriasis on the Scalp During the Acute Phase or From Induction to Remission[a]

Treatment	Evidence Level	Balance of Desirable and Undesirable Effects	Resource Utilization	Patient Comfort	Strength of Recommendation
Corticosteroids (lotion)	High	Good	High	Moderate	A
Corticosteroids (shampoo)	High	Good	Moderate	Good	A
Corticosteroids (foam)	Moderate	Good	Moderate	Moderate	B
Vitamin D analogs	High	Moderate	Moderate	Moderate	B
Topical retinoids	Very low	Moderate	Moderate	Poor	D
Combination of corticosteroids and calcipotriol	High	Good	Moderate	Moderate	A
Combination corticosteroids and salicylates	Low	Moderate	High	Moderate	C
Coal tar	Moderate	Moderate	Moderate	Poor	C
Salicylates	Low	Moderate	High	Moderate	C
Antifungal agents	Very low	Poor	Moderate	Moderate	D
Phototherapy	Low	Moderate	Low	Poor	D
Systemic agents	Low	Moderate	Very low	Moderate	D

[a]Five levels of evidence and 4 grades of recommendation (A to D) were defined.
Grade A (highly recommended), based on level 1 studies. Grade B (favorable recommendation), based on level 2 or 3 studies or extrapolations from level 1 studies. Grade C (inconclusive favorable recommendation), based on level 4 studies. Grade D, which implies neither recommendation or disapproval of the intervention, based on level 5 studies.

Table 14 GRADE Recommendations of the Panel of Experts for the Topical Treatment of Psoriasis of the Scalp During the Maintenance Phase[a]

Treatment	Evidence Level	Balance of Desirable and Undesirable Effects	Resource Utilization	Patient Comfort	Strength of Recommendation
Corticosteroids (lotion)	Very low	Unknown	Moderate	Moderate	D
Corticosteroids (shampoo)	Very low	Unknown	Moderate	High	D
Corticosteroids (foam)	Very low	Unknown	Moderate	Moderate	D
Vitamin D analogs	High	Good	Moderate	Moderate	A
Topical retinoids	Very low	Unknown	Moderate	Poor	D
Combination corticosteroids and calcipotriol	High	Good	Moderate	Moderate	A
Combination corticosteroids and salicylates	Low	Unknown	Moderate	Moderate	D
Coal tar	Low	Poor	Moderate	Poor	D
Salicylates	Low	Unknown	Moderate	Poor	D
Antifungal agents	Very low	Poor	Moderate	Moderate	D
Phototherapy	Very low	Moderate	Low	Poor	D
Systemic agents	Low	Moderate	Very low	Moderate	D

[a]Five levels of evidence and 4 grades of recommendation (A to D) were defined.
Grade A (highly recommended), based on level 1 studies. Grade B (favorable recommendation), based on level 2 or 3 studies or extrapolations from level 1 studies. Grade C (inconclusive favorable recommendation), based on level 4 studies. Grade D, which implies neither recommendation or disapproval of the intervention, based on level 5 studies.

induction and maintenance are shown in Tables 13 and 14, respectively.

Conflict of Interest

Dr Luis Puig has received consulting and speaking fees and has participated in clinical trials sponsored by Leo Pharma and Galderma.

Dr Miquel Ribera has received consulting and speaking fees and has participated in clinical trials sponsored by Leo Pharma, Galderma, Abbott, Janssen-Cilag, Merck-Serono, Novartis, Pfizer, Schering-Plough, and Wyeth.

Dr José M. Hernánz has received consulting and speaking fees and has participated in clinical trials sponsored by Leo Pharma, Abbott, Janssen, Leo Pharma, Merck-Serono, Novartis, Pfizer, Schering-Plough, and Wyeth.

Dr Isabel Belinchón has received consulting and speaking fees and has participated in clinical trials sponsored by Leo Pharma, Abbott, Janssen, Leo Pharma, Merck-Serono, Novartis, Pfizer, Schering-Plough, and Wyeth.

Dr Esteve Colomé and Dr Gloria Caballé are employees of Leo Pharma España, a company that sponsored the meetings and teleconferences of this group without in any way interfering in those meetings.

The remaining authors declare no conflicts of interest.

References

1. Farber EM, Nail L. Natural history and treatment of scalp psoriasis. Cutis. 1992;49:396-400.
2. Van de Kerkhof PC, Franssen ME. Psoriasis of the scalp. Diagnosis and Management. Am J Clin Dermatol. 2001;2: 159-65.
3. Sola-Ortigosa J, Sánchez-Regaña M, Umbert-Millet P. Psoriasis del cuero cabelludo. Actas Dermosifiligr. 2009;100:536-43.
4. Van de Kerkhof PC, de Hoop D, de Korte J, Kuipers MV. Scalp psoriasis, clinical presentations and therapeutic management. Dermatology. 1998;197:326-34.
5. Heydendael VM, de Borgie CA, Spuls PL, Bossuyt PM, Bos JD, de Rie MA. The burden of psoriasis is not determined by disease severity only. J Investig Dermatol Symp Proc. 2004;9:131-5.
6. Harbour R, Miller J, for the Scottish Intercollegiate Guidelines Network Grading Review Group. A new system for grading recommendations in evidence based guidelines. BMJ. 2001;323:334-6.
7. Chan CS, Van Voorhees AS, Lebwohl MG, Korman NJ, Young M, Bebo BF, et al. Treatment of severe scalp psoriasis: from the medical board of the National Psoriasis Foundation. J Am Acad Dermatol. 2009;60:962-71.
8. Papp K, Berth-Jones J, Kragballe K, Wozel G, de la Brassinne. Scalp psoriasis: a review of current topical treatments options. J Eur Acad Dermatol Venereal. 2007;21:1151-60.
9. Mason AR, Mason J, Cork M, Dooley G, Edwards G. Topical treatments for chronic plaque psoriasis. Cochrane Database Sys Rev. 2009;CD005028.
10. Ortonne J, Chimenti S, Luger T, Puig L, Reid F, Trüeb R. Scalp psoriasis: European consensus on grading and treatment algorithm. J Eur Acad Dermatol Venereol. 2009;23:1435-44.
11. Jones J, Hunter D. Consensus methods for medical and health services research. BMJ. 1995;311:376-80.
12. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. BMJ. 2004;328:1490.
13. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE Working Group GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336:924-6.
14. Frederiksson T, Pettersson U. Severe psoriasis—oral therapy with a new retinoid. Dermatologica. 1978;157:238-44.
15. Reich K, Mrowietz U. Treatment goals in psoriasis. J Dtsch Dermatol Ges. 2007;5:566-74.
16. Thaçi D, Daiber W, Boehncke WH, Kaufmann R. Calcipotriol solution for the treatment of scalp psoriasis: evaluation of efficacy, safety and acceptance in 3396 patients. Dermatology. 2001;203:153-6.
17. Choi J, Koo JY. Quality of life issues in psoriasis. J Am Acad Dermatol. 2003;49(Suppl 2):S57-61.
18. Ware JE, Kosinski M, Turner-Bowker DM, Gandek B. How to score version 2 of the SF-36 Health Survey. QualityMetric Incorporated, Lincoln, Rhode Island 2000.
19. Jones-Caballero M, Fernández- Peñas P, García-Díez A, Chren MM, Badía X. La versión española de Skindex-29. Un instrumento de medida de la calidad de vida en pacientes con enfermedades cutáneas. Med Clin (Barc). 2002;118:5-9.
20. Chen SC, Yeung J, Chren MM. Scalpdex: a quality-of-life instrument for scalp dermatitis. Arch Dermatol. 2002;138: 803-7.
21. Lebwohl M. A clinician's paradigm in the treatment of psoriasis. J Am Acad Dermatol. 2005;53(Suppl 1):S59-69.
22. Frangos JE, Kimball AB. Clobetasol propionate emollient formulation foam in the treatment of corticosteroid-responsive dermatoses. Expert Opin Pharmacother. 2008;9: 2001-7.
23. Lepaw MI. Double-blind comparison of halcinonide solution and placebo control in treatment of psoriasis of the scalp. Cutis. 1978;21:571-3.
24. Olsen EA, Cram DL, Hickman JG, Jacobson C, Jenkins EE, Lasser AE, et al. A double-blind, vehicle-controlled study of clobetasol propionate 0.05% (Temovate) scalp application in the treatment of moderate to severe scalp psoriasis. J Am Acad Dermatol. 1991;24:443-7.
25. Pauporte M, Maibach H, Lowe N, Pugliese M, Friedman DJ, Mendelsohn H, et al. Fluocinolone acetonide topical oil for scalp psoriasis. J Dermatolog Treat. 2004;15:360-4.
26. Jarrat M, Breneman D, Gottlieb AB, Poulin Y, Liu Y, Foley V. Clobetasol propionate shampoo 0.05%: a new option to treat patients with moderate to severe scalp psoriasis. J Drugs Dermatol. 2004;3:367-73.
27. Franz TJ, Parsell DA, Halualani RM, Hannigan JF, Kalbach JP, Harkonen S. Betamethasone valerate foam 0.12%: a novel vehicle with enhanced delivery and efficacy. Int J Dermatol. 1999;38:628-32.
28. Andreassi L, Giannetti A, Milani M. Efficacy of betamethasone valerate mousse in comparison with standard therapies on scalp psoriasis. An open, multicentre, randomized, controlled, cross-over study on 241 patients. Br J Dermatol. 2003;148: 134-8.
29. Katz HI, Lindholm JS, Weiss JS, Shavin JS, Morman M, Bressinck R, et al. Efficacy and safety of twice-daily augmented betamethasone dipropionate lotion versus clobetasol propionate solution in patients with moderate-to-severe scalp psoriasis. Clin Ther. 1995;17:390-401.
30. Breneman DL, Davis M, Berger V, Chaney R. A double blind trial comparing the efficacy and safety of augmented betamethasone dipropionate lotion with fluocinonide solution in the treatment of severe scalp psoriasis. J Dermatol Treat. 1992;3:19-21.

31. Feldman SR, Ravis SM, Fleischer AB, McMichael A, Jones E, Kaplan R, et al. Betamethasone valerate in foam vehicle is effective with both daily and twice a day dosing: a single-blind, open-label study in the treatment of scalp psoriasis. J Cutan Med Surg. 2001;5:386-9.
32. Vanderploeg DE, Cornell RC, Binder R, Weintraub JS, Jarrat M, Jones ML, et al. Clinical trial in scalp psoriasis. Mometasone furoate 0.1% applied once daily vs betamethasone valerate lotion 0.1% applied twice daily. Acta Ther. 1989;15:145-52.
33. Swinehart JM, Barkoff JR, Dvorkin D, Fisher G, Peets E. Mometasone furoate lotion once daily versus triamcinolone acetonide lotion twice daily in psoriasis. Int J Dermatol. 1989;28:680-1.
34. Reygagne P, Mrowietz U, Decroix J, de Waard-van der Spek FB, Acebes LO, Figueiredo A, et al. Clobetasol propionate shampoo 0.05% and calcipotriol solution 0.005%: a randomized comparison of efficacy and safety in subjects with scalp psoriasis. J Dermatolog Treat. 2005;16:31-6.
35. Klaber MR, Hutchinson PE, Pelvis-Leftick A, Kragballe K, Reunala TL, van de Kerkhof PC, et al. Comparative effects of calcipotriol solution (50 micrograms/mL) and betamethasone 17-valerate solution (1mg/mL) in the treatment of scalp psoriasis. Br J Dermatol. 1994;131:678-83.
36. Griffiths CE, Finlay AY, Fleming CJ, Barrer JN, Mizzi F, Arsonnaud S. A randomized, investigator-masked clinical evaluation of the efficacy and safety of clobetasol propionate 0.05% shampoo and tar blend 1% shampoo in the treatment of moderate to severe scalp psoriasis. J Dermatolog Treat. 2006;17:90-5.
37. Hillström L, Pettersson L, Svensson L. Comparison of betamethasone dipropionate lotion with salicylic acid (Diprosalic) and clobetasol propionate lotion (Dermovate) in the treatment of psoriasis of the scalp. J Int Med Res. 1982; 10:419-22.
38. Andres P, Poncet M, Farzaneh S, Soto P. Short-term safety assessment of clobetasol propionate 0.05% shampoo: hypothalamic-pituitary-adrenal axis suppression, atrophogenicity, and ocular safety in subjects with scalp psoriasis. J Drugs Dermatol. 2006;5:328-32.
39. Lassus A. Local treatment of psoriasis of the scalp with clobetasol propionate and betamethasone-17,21-dipropionate: a double-blind comparison. Curr Med Res Opin. 1976;4:365-7.
40. Bovenschen H, van de Kerkhof P. Treatment of scalp psoriasis with clobetasol-17 propionate 0.05% shampoo: a study on daily clinical practice. J Eur Acad Dermatol Venereol. 2010;24:439-44.
41. Tan J, Thomas R, Wang B, Gratton D, Vender R, Kerrouche N, et al. Short-contact clobetasol propionate shampoo 0.05% improves quality of life in patients with scalp psoriasis. Cutis. 2009;83:157-64.
42. Kragballe K, Wildfang IL. Calcipotriol (MC 903), a novel vitamin D3 analogue stimulates terminal differentiation and inhibits proliferation of cultured human keratinocytes. Arch Dermatol Res. 1990;282:164-7.
43. Green C, Ganpule M, Harris D, Kavanagh G, Kennedy C, Mallet R, et al. Comparative effects of calcipotriol (MC903) solution and placebo (vehicle of MC903) in the treatment of psoriasis of the scalp. Br J Dermatol. 1994;130:483-7.
44. Klaber MR, McKinnon C. Calcipotriol (Dovonex®) scalp solution in the treatment of scalp psoriasis: comparative efficacy with 1% coal tar/1% coconut oil/0.05% salicylic acid (Capasal®) shampoo, and long-term experience. J Dermatolog Treat. 2000;11:21-8.
45. Duweb GA, Abuzariba O, Rahim M, Al-Taweel M, Abdulla SA. Scalp psoriasis: topical calcipotriol 50 μg/g/ml solution vs betamethasone valerate 1% solution. Int J Clin Pharmacol Res. 2000;20:65-8.
46. Emaitig S, Alyazachi M, Bashir A, Duweb G. Calcipotriol solution vs. betamethasone and salicylic acid solution in the treatment of scalp psoriasis. J Eur Acad Dermatol Venereol. 2004;18(Suppl 2):262.
47. Barrett C, Lowson D, Blades KJ. Limited benefit of combined use of tar-based shampoo with 50 mg/ml calcipotriol solution in scalp psoriasis. J Dermatol Treat. 2005;16:175.
48. Ruzicka T, Trompke C. Behandlung der Kopfhaut-Psoriasis. Gute Wirksamkeit und Sicherheit durch Tacalcitol-Emulsion. Hautarzt. 2004;55:165-70.
49. Barnes L, Altmeyer P, Fôrstrôm L, Stenström MH. Long-term treatment of psoriasis with calcipotriol scalp solution and cream. Eur J Dermatol. 2000;10:199-204.
50. Faergemann J, Diehl U, Bergfelt L, Brodd A, Edmar B, Hersle K, et al. Scalp psoriasis: synergy between the Malassezia yeasts and skin irritation due to calcipotriol. Acta Derm Venereol. 2003;83:438-41.
51. Ramsay CA, Berth-Jones J, Brundin G, Cunliffe WJ, Dubertret L, Van de Kerkhof PC, et al. Long-term use of topical calcipotriol in chronic plaque psoriasis. Dermatology. 1994;189:260-4.
52. Koo J. Vitamin D and scalp psoriasis. Cutis. 2002;70 (Suppl 5): 21-4.
53. Kragballe K, Van de Kerkhof PC. Consistency of data in six phase III clinical studies of a two-compound product containing calcipotriol and betamethasone dipropionate ointment for the treatment of psoriasis. J Eur Acad Dermatol Venereol. 2006;20:39-44.
54. Cassano N, Vena GA. Treatment of scalp psoriasis with betamethasone dipropionate and calcipotriol two-compound product. Acta Derm Venereol. 2007;87:85-6.
55. Downs AM. Dovobet ointment under occlusion overnight for troublesome scalp psoriasis. Acta Derm Venereol. 2006;86:57-8.
56. Emerson RM, Howlett C. Successful treatment of scalp psoriasis with Dovobet® ointment. Br J Dermatol. 2004;151 (Supl 68):52-3.
57. Buckley C, Hoffmann V, Shapiro J, Saari S, Cambazard F, Milsgaard M. Calcipotriol plus betamethasone dipropionate scalp formulation is effective and well tolerated in the treatment of scalp psoriasis: A phase II study. Dermatology. 2008;217:107-13.
58. Jemec GBE, Ganslandt C, Ortonne JP, Poulin Y, Burden AD, de Unamuno P, et al. A new scalp formulation of calcipotriene plus betamethasone compared with its active ingredients and the vehicle in the treatment of scalp psoriasis: a randomized, double-blind, controlled trial. J Am Acad Dermatol. 2008; 59:455-63.
59. Van de Kerkhof PCM, Hoffmann V, Anstey A, Barnes L, Bolduc C, Reich K, et al. A new scalp formulation of calcipotriol plus betamethasone dipropionate compared with each of its active ingredients in the same vehicle for the treatment of scalp psoriasis: a randomized, double-blind, controlled trial. Br J Dermatol. 2009;160:170-6.
60. Tyring S, Bibby A. Calcipotrione/betamethasone dipropionate gel compared to gel vehicle in treating scalp psoriasis in Hispanic/Latino and black/African American patients. J Am Acad Dermatol. 2008;58(Suppl 2):AB125.
61. Ortonne JP, Ganslandt C, Tan J, Nordin P, Kragballe K, Segaert S. Quality of life in patients with scalp psoriasis treated with calcipotriol/betamethasone dipropionate scalp formulation: a randomized controlled trial. J Eur Acad Dermatol Venereol. 2009;23:919-26.
62. Kragballe K, Hoffmann V, Ortonne JP, Tan J, Nordin P, Segaert S. Efficacy and safety of calcipotriol plus betamethasone dipropionate scalp formulation compared with calcipotriol scalp solution in the treatment of scalp psoriasis: a randomized controlled trial. Br J Dermatol. 2009;161:159-66.

63. Luger TA, Cambazard F, Larsen FG, Bourcier M, Gupta G, Clonier F, et al. A study of the safety of efficacy of calcipotriol and betamethasone dipropionate scalp formulation in the long-term management of scalp psoriasis. Dermatology. 2008;217:321-8.
64. López Estebaranz JL. Tratamiento local de la psoriasis del cuero cabelludo del adulto. Monogr Dermatol. 2009;22: 55-60.
65. Going SM, Guyer BM, Jarvie DR, Hunter JA. Salicylic acid gel for scalp psoriasis. Clin Exp Dermatol. 1986;11:260-2.
66. Langner A, Wolska H, Hebborn P. Treatment of psoriasis of the scalp with coal tar gel and shampoo preparations. Cutis. 1983;32:290-6.
67. McGill A, Frank A, Emmett N, Turnbull DM, Birch-Machin MA, Reynolds NJ. The anti-psoriatic drug anthralin accumulates in keratinocyte mitochondria, dissipates mitochondrial membrane potential, and induces apoptosis through a pathway dependent on respiratory component mitochondria. FASEB J. 2005;19:1012-24.
68. Wulff-Woesten A, Ohlendorf D, Henz BM, Haas N. Dithranol in an emulsifying oil base (bio-wash-oil) for the treatment of psoriasis of the scalp. Skin Pharmacol Physiol. 2004;17:91-7.
69. Gollnick HP, Finzi AF, Marks R, Barker JN, Jansen C, Revuz J, et al. Optimising the use of tazarotene in clinical practice: consensus statement from the European advisory panel for tazarotene (Zorac TM). Dermatology. 1999;199:40-6.
70. Gueho E, Boekhout T, Ashbee HR, Guillot J, Van Belkum A, Faergemann J. The role of the Malassezia species in the ecology of human skin and as pathogens. Med Mycol. 1998; 36(Suppl 1):220-9.
71. Warren RB, Brown BC, Griffiths CE. Topical treatment for scalp psoriasis. Drugs. 2008;68:2293-302.
72. Shemer A, Nathansohn N, Kaplan B, Weiss G, Newman N, Trau H. Treatment of scalp seborrheic dermatitis and psoriasis with an ointment of 40% urea and 1% bifonazole. Int J Dermatol. 2000;39:532-4.
73. Jury CS, McHugh L, Shankland GS, Burden AD. A randomized, placebo-controlled trial of oral itraconazole in scalp psoriasis. J Dermatol Treat. 2000;11:85-9.
74. Faergemann J, Diehl U, Bergfelt L, Brodd A, Edmar B, Hersle K, et al. Scalp psoriasis: synergy between the Malassezia yeasts and skin irritation due to calcipotriol. Acta Derm Venereol. 2003;83:438-41.
75. Wheeler LA, Saperstein MD, Lowe NJ. Mutagenicity of urine from psoriatic patients undergoing treatment with coal tar and ultraviolet light. J Invest Dermatol. 1981;77:181-5.
76. Yuspa SH. Cutaneous chemical carcinogenesis. J Am Acad Dermatol. 1986;15:1031-44.
77. Johnson C, Edison B, Brouda I, Green B. A novel LCD (coal tar) solution for psoriasis does not discolor naturally light or color-processed hair in an exaggerated exposure test model. J Cosmet Dermatol. 2009;8:211-5.
78. Carrascosa JM, Vanaclocha F, Borrego L, Fernández-López E, Fuertes A, Rodríguez-Fernández-Freire L, et al. Revisión actualizada del tratamiento tópico de la psoriasis. Documento de Consenso. Actas Dermosifiliogr. 2009;100:190-200.
79. Dando TM, Wellington K. Topical tazarotene: a review of its use in the treatment of plaque psoriasis. Am J Clin Dermatol. 2005;6:255-72.
80. Taylor CR, Racette AL. A 308-nm excimer laser for the treatment of scalp psoriasis. Lasers Surg Med. 2004;34:136-40.
81. Dotterud LK, Braun R. UV-B comb versus betamethasone solution in scalp psoriasis. Tidsskr Nor Laegeforen. 2000; 120:1858-9.
82. Lindelöf B, Johannesson A. Psoriasis of the scalp treated with Grenz rays or topical corticosteroid combined with Grenz rays. A comparative randomized trial. Br J Dermatol. 1988;119:241-4.
83. García Díez A. Tratamiento sistémico de la psoriasis del cuero cabelludo. Monogr Dermatol. 2009;22:61-6.
84. Heydendael VM, Spuls PI, Opmeer BC, de Boggie CA, Reitsma JB, Goldschmidt WF, et al. Methotrexate versus cyclosporine in moderate-to-severe chronic plaque psoriasis. N Engl J Med. 2003;349:658-65.
85. Flyström I, Stenberg B, Svensson A, Bergbrant IM. Methotrexate vs ciclosporin in psoriasis: effectiveness, quality of life and safety. A randomized controlled trial. Br J Dermatol. 2008;158:116-21.
86. Saurat JH, Stingl G, Dubertret L, Papp K, Langley RG, Ortrone JP, et al. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs methotrexate vs placebo in patients with psoriasis (CHAMPION). Br J Dermatol. 2008;158:558-66.
87. Koo J. A randomized, double-blind study comparing the efficacy, safety and optimal dose of two formulations of cyclosporine, Neoral and Sandimmun, in patients with psoriasis. Br J Dermatol. 1998;139:88-95.
88. Ellis CN, Fradin MS, Messana JM, Brown MD, Siegel MT, Hartley AH, et al. Cyclosporine for plaque-type psoriasis. Results of a multidose, double-blind trial. N Eng J Med. 1991;324:277-84.
89. Kragballe K, Cansen CT, Geiger JM, Bjerke JR, Falk ES, Gip L, et al. A double-blind comparison of acitretin and etretinate in the treatment of severe psoriasis. Results of a Nordic multicentre study. Acta Derm Venereol. 1989;69:35-40.
90. Pearce DJ, Klinger S, Ziel KK, Murad EJ, Rowell R, Feldman SR. Low-dose acitretin is associated with fewer adverse events than high-dose acitretin in the treatment of psoriasis. Arch Dermatol. 2006;142:1000-4.
91. Altmeyer PJ, Matthes U, Pawlak F, Hoffmann K, Frosch PJ, Ruppert P, et al. Antipsoriatic effect of fumaric acid derivates. Results of a multicenter double-blind study in 100 patients. J Am Acad Dermatol. 1994;30:977-81.
92. Gollnick H, Altmeyer P, Kaufmann R, Ring J, Christophers E, Pavel S, et al. 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. 2002;205:46-53.
93. Gordon KB, Langley RG, Leonardi C, Toth D, Menter MA, Kang S, et al. Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: a double-blind, randomized controlled trial and open-label extension study. J Am Acad Dermatol. 2006;55:598-606.
94. Menter A, Tyring SK, Gordon K, Kimball AB, Leonardi C, Langley RG, et al. Adalimumab therapy for moderate to severe psoriasis: a randomized, controlled phase III trial. J Am Acad Dermatol. 2008;58:106-15.
95. Thaçi D, Khemis A, Ghislain P-D, Arenberger P, Kragballe K, Saurat J-H, et al. Adalimumab plus topical treatment (calcipotriol/beta-methasone) in the treatment of moderate to severe psoriasis – Effects on skin, scalp, and nails: Results from BELIEVE. 18th Congress of the European Academy of Dermatology and Venereology (EADV), Berlin, 2009; Abstract P824.
96. Gottlieb AB, Matheson RT, Lowe N, Krueger GG, Kang S, Goffe BS, et al. A randomized trial of etanercept as monotherapy for psoriasis. Arch Dermatol. 2003;139:1627-32.
97. Leonardi CL, Powers JL, Matheson RT, Goffe BS, Zitnik R, Wang A, et al. Etanercept as monotherapy in patients with psoriasis. N Eng J Med. 2003;349:2014-22.
98. Papp KA, Tyring S, Lahfa M, Prinz J, Griffiths CE, Nakanishi AM, et al. A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. Br J Dermatol. 2005;152:1304-12.

99. Tyring S, Gottlieb A, Papp K, Gordon K, Leonardi C, Wang A, et al. Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. Lancet. 2006;367:29-35.
100. Ortonne JP, Strohal R, Dauden E, Robertson D, Pedersen R, Molta C. Etanercept treatment for up to 54 weeks sustain scalp improvement in patients with moderate to severe psoriasis: Results of the Crystel Study. 5th European Academy of Dermatology and Venereology (EADV) Spring Symposium, Istanbul, 22–25 May 2008. Abstract #FC08-5.
101. Chaudari U, Romano P, Mulcahy LD, Dooley LT, Baker DJ, Gottlieb AB. Efficacy and safety of infliximab monotherapy for plaque-type psoriasis: a randomised trial. Lancet. 2001; 357:1842-7.
102. Gottlieb AB, Evans R, Li S, Dooley T, Guzzo CA, Baker D, et al. Infliximab induction therapy for patients with severe plaque-type psoriasis: a randomized, double-blind, placebo-controlled trial. J Am Acad Dermatol. 2004;51:534-42.
103. Ortonne JP. Clinical response to alefacept: results of a phase 3 study of intramuscular administration of alefacept in patients with chronic plaque psoriasis. J Eur Acad Dermatol Venereol. 2003;17(Suppl 2):12-6.
104. Gribetz CH, Blum R, Brady C, Cohen S, Lebwohl M. An extended 16-week course of alefacept in the treatment of chronic plaque psoriasis. J Am Acad Dermatol. 2005;53: 73-5.
105. Krell J, Nelson C, Spencer L, Miller S. An open-label study evaluating the efficacy and tolerability of alefacept for the treatment of scalp psoriasis. J Am Acad Dermatol. 2008;58:609-16.
106. Leonardi CL, Kimball AB, Papp KA, Yeilding N, Guzzo C, Wang Y, et al, for the PHOENIX 1 Study Investigators. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double blind, placebo-controlled trial (PHOENIX 1). Lancet. 2008;371:1665-74.
107. Papp K, Langley RG, Lebwohl R, Krueger GG, Szapary P, Yeilding N, et al, for the PHOENIX 2 Study Investigators. 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. 2008;371:1675-84.
108. El Shabrawi-Caelen L, La Placa M, Vincenci C, Haidn T, Muelleger R, Tosti A. Adalimumab-induced psoriasis of the scalp with diffuse alopecia: A severe potentially irreversible cutaneous side effect of TNF-alpha blockers. Inflamm Bowel Dis. 2010;16:182-3.
109. Barlett BL, Tyring SK. Ustekinumab for chronic plaque psoriasis. Lancet. 2008;371:1639-40.