

Title: Topical Treatments for Chronic Plaque Psoriasis of the Scalp: a Systematic Review
Running head: Topical Treatments for Chronic Plaque Psoriasis of the Scalp

Word counts:

222 / 250 (abstract);

2710 / 3000 (main body);

64 / 70 (summary)

Tables: 2

Figures: 4

Authors: AR Mason ^{1*}; JM Mason ²; MJ Cork ³; H Hancock ²; G Dooley ⁴

¹ Centre for Health Economics, University of York, York, YO10 5DD, UK

² School of Medicine, Pharmacy and Health, Durham University, Stockton-on-Tees, UK

³ Academic Unit of Dermatology Research, University of Sheffield Medical School, Sheffield, UK

⁴ Metaxis Ltd, Curbridge, UK

* Corresponding author:

Anne Mason, Centre for Health Economics, University of York, York, YO10 5DD, UK.

Tel: +44(0)1904 321432; Fax: +44(0)1904 321402; Email: anne.mason@york.ac.uk

Funding sources:

The Psoriasis Association, UK. The funder had no involvement in study design, data collection, data analysis, manuscript preparation or publication decisions.

Conflict of interest statement: None declared

Disclaimer: The results of a Cochrane review can be interpreted differently, depending on people's perspectives and circumstances. The conclusions presented are the opinions of review authors and are not necessarily shared by The Cochrane Collaboration

Summary

What is already known about this topic?

- Psoriasis of the scalp affects up to 79% of people with chronic plaque psoriasis.
- Despite the range of treatment options, psoriasis of the scalp is a difficult condition to manage.

What does this study add?

- Very potent corticosteroids are more effective than potent steroids and vitamin D analogues either as monotherapy or combination therapy. However, the atrophic potential of corticosteroid treatments for scalp psoriasis remains uncertain.

Abstract

Background

Chronic plaque psoriasis is the most common type of psoriasis and is characterised by redness, thickness and scaling. First line management is with topical treatments.

Objective

Our objective was to establish the effectiveness, tolerability and safety of topical treatments for people with chronic plaque psoriasis of the scalp, assessing placebo-controlled trials of all treatments and head-to-head trials that assessed vitamin D analogues.

Methods

As part of a Cochrane review of topical treatments for psoriasis we systematically searched electronic databases for randomized controlled trials. The review included 26 randomised controlled trials of treatments for psoriasis of the scalp with 8,020 participants. Trials used several measures to assess changes in psoriasis severity: these were combined using the standardised mean difference metric and interpreted by reporting as a 6-point global improvement score.

Results

On effectiveness grounds, very potent or potent steroid treatments should be preferred to vitamin D3 analogue with approximately an average 10% additional improvement on a 6-point scale. Vitamin D3 analogue combined with potent steroid appears more effective than monotherapy with either vitamin D3 or steroids. Rates of withdrawal from treatment and adverse events in trials were generally low and similar to those for placebo. There remains uncertainty about the atrophic potential of corticosteroid treatments for scalp psoriasis.

Conclusions

Corticosteroids are more effective as vitamin D analogues and similarly tolerated. However, further research is needed to inform long-term maintenance treatment and provide appropriate safety data.

Key words: Psoriasis; Review; Drug Administration, Topical; Treatment Outcome; Drug Safety

Background

Psoriasis is a chronic inflammatory skin disease with a prevalence ranging from 1-2% in the UK and northern European populations^{1,2} down to 0.1 to 0.3% in the Far East³ and China.⁴ Chronic plaque psoriasis may be localised or widespread and accounts for 90% of psoriasis cases;⁵ it is characterised by red patches of thickened skin (plaques) covered in silver scales. Any area of the body may be affected, but the main areas are the knees, elbows, lower back and scalp. There is a wide spectrum of disease severity from a single plaque to involvement of more than 90% of the skin surface. Psoriasis can lead to social isolation,⁶ stigmatisation⁷ and can adversely affect quality of daily life.⁸⁻¹⁵ Psoriasis of the scalp affects up to 79% of people with chronic plaque psoriasis; the scalp is typically the first area of the body to be affected, and the frequency of involvement increases with the duration of the disease.¹⁶

Disease progression is complex and appears to be influenced by many factors including local trauma, infections, certain drugs (such as beta-blockers, lithium, chloroquine and non-steroidal anti-inflammatory drugs (NSAIDs)), the duration of antipsoriatic treatments, endocrine factors, sunlight, alcohol, smoking and stress.¹⁷ The skin lesions of psoriasis are characterised by cells multiplying too quickly (epidermal hyperproliferation), cells not maturing normally (abnormal keratinocyte differentiation) and the presence of cells which cause inflammation (a lymphocyte inflammatory infiltrate).¹⁸⁻²⁰ Psoriasis is now recognised as an immune-mediated disorder, with tumour necrosis factor alpha (TNF α), dendritic cells and T-cells all contributing to its pathogenesis.²¹ A meta-analysis²² of three genome-wide association studies (GWAS) identified 15 new chromosomal susceptibility loci for psoriasis, bringing the total number of loci known to be associated with psoriasis to 36. Several of these loci are involved in the regulation of the skin's innate immune response. They provide confirmation of the role of several existing biologic therapies and provide new targets for drug development.

Topical treatments are the main therapy for psoriasis of the scalp, whatever the level of disease severity.¹⁶ They include vitamin D analogues, used alone or in combination with potent corticosteroids; potent and very potent corticosteroids; coal tar; and other treatments.^{23 24} Scalp psoriasis is one of the most challenging forms of the disease to manage, because the presence of hair makes the use of ointments and cream-based products “difficult and messy”.²⁵ Lotions, shampoos, gels and sprays are all used as vehicles for active treatment.

This paper is based on a Cochrane review^{26 27} most recently substantially amended in The Cochrane Library 2013, Issue (3) (see <http://www.thecochranelibrary.com>).²⁸ Cochrane reviews are regularly updated as new evidence emerges and in response to feedback; the Cochrane Library should be consulted for the full and most recent version of the review.

Objective

To compare the effectiveness, tolerability and safety of topical treatments for people with chronic plaque psoriasis of the scalp relative to placebo, and to compare vitamin D analogues head-to-head with other topical treatments.

Methods

This research presents a subset of a larger Cochrane review on topical treatments for chronic plaque psoriasis (*Mason 2013, in press*).²⁸ The full review includes 177 studies, reported in 242 articles. The methods reported here are those used for the full review, including trials of body and scalp psoriasis.

Inclusion criteria

We included only randomised controlled trials in the review. Trials could be either placebo-controlled or have an active comparison with a vitamin D preparation. We selected vitamin D analogues for this comparison because they are first-line treatments in many developed countries.²⁹ Trials of systemic or ultra-violet (phototherapy) treatments with adjunctive topical treatment were not eligible for inclusion. We excluded the study if no useful effectiveness, withdrawal or adverse

events data were available, either from the published paper or from sponsors or trialists, we excluded the study.

Data extraction

One author extracted study data and assessed study quality. A second author checked these data.

Searches

Table 1 shows the electronic databases searched in February 2011. Details of the search strategy for Medline are available as an online appendix (Ref). Ongoing studies were identified from the UK Clinical Research Network Study Portfolio and the metaRegister of Current Controlled Trials. We routinely contacted trialists and companies for missing data.

TABLE 1 HERE

Outcomes

We extracted data from trials on four primary outcomes (Table 2). Trials often reported more than one measure, but no trial reported all of the measures. We therefore devised a 'combined endpoint' to facilitate treatment comparisons, and use this to report summary findings from the review. We constructed the combined endpoint by taking primary outcomes data in the order listed in Table 2, according to availability. Thus within-trial differences essentially capture a common construct of change in psoriasis severity due to treatment, regardless of the outcome measure used. Additionally we extracted data on five secondary outcomes: data on withdrawal due to any cause, to adverse events and to treatment failure, as well as adverse events due to local and systemic effects.

TABLE 2 HERE

Statistical Methods

We analysed and pooled findings using a standardised mean difference (SMD) statistic within a random effects model. We report heterogeneity Q (χ^2) statistic and I^2 statistics, noting heterogeneity according to the Cochrane Handbook's "rough guide to interpretation": 50% to 90%: may represent substantial heterogeneity and 75% to 100% considerable heterogeneity.³⁰ Where studies did not report estimates of variance, we derived them from confidence intervals or from P values where possible, or imputed them deterministically by pooling the standard deviations of treatment cohorts fully reported in trials and adjusted for scale. SMD combined endpoints were transformed back to natural units on a 6-point improvement (Investigators Global Assessment of improvement; IAGI) scale (ranging from 'worse' to 'clearance') using pooled IAGI standard deviations. As definitions of withdrawal and adverse events vary between trials, data were summarised using a random effects risk difference metric.

Interpretation

Interpreting the weight of evidence in support of a treatment is ultimately arbitrary, nonetheless there are two accepted principles (all things being equal): first, consistent findings from multiple independent trials provide stronger evidence than one trial alone; and second, trials with larger numbers of patients are preferable to smaller ones because of the lower risk of inferential error. These two principles are used to interpret available evidence for the clinical management of scalp psoriasis. The statistical significance of findings was determined at the 5% level.

Results

The review included 26 trials of scalp psoriasis:³¹⁻⁵⁶ 14 trials were placebo controlled only; 11 compared vitamin D with other active treatment; and, one additional trial⁴¹ reported both placebo-controlled and active comparisons. Table 3 summarises the characteristics of the scalp trials reviewed.

TABLE 3 HERE

Of the 20 trials that reported baseline disease severity, the majority (13/20, 65%) investigated moderate to severe psoriasis of the scalp (Figure 1).

FIGURE 1 HERE

Treatment duration averaged 7 weeks, but ranged from 2 weeks to 52 weeks. With the exception of one within-patient (right-left) study that was published in 1978,⁴⁷ trials were between-patient (parallel group) in design.

FIGURE 2 HERE

Figure 2 summarises study quality. Most trials (73%) were double-blind. Single-blind (investigator only; 2 trials) and 'open' (no blinding; 3 trials) studies were typically those in which it was impossible to conceal the identity of products being investigated from participants, for example, trials of coal tar products, or trials of products comparing different vehicle formulations such as shampoo and solution. The majority of studies did not report their methodology in sufficient detail. For instance, just 8 trials (31%) clearly reported the randomisation method, and concealment of treatment allocation was unclear in 25 trials (96%). In one trial, concealment of treatment allocation was 'adequate' (i.e. the investigator could not foresee treatment assignment). On average, 11% of patients were lost to follow up during trials (range 0% to 21%). However, most trials (73%) demonstrated that groups were comparable in both clinical and demographic characteristics.

Placebo-controlled trials

We found placebo-controlled evidence of effectiveness for 11 treatments for scalp psoriasis (Figure 3). Thirteen between-patient trials and one within-patient trial⁴⁷ contributed data from 3011 participants. Patient participation in the trials ranged between two and eight weeks.

FIGURE 3 HERE

The largest treatment effect was observed for the very potent corticosteroid clobetasol propionate, reported in 4 trials (SMD -1.57; 95% CI -1.81 to -1.34; $I^2 = 43.3\%$; N=788), which improved participants' psoriasis by 1.9 points on a 6-point global improvement scale. The potent steroid betamethasone dipropionate, reported in 2 trials (SMD -1.09; 95% CI -1.29 to -0.90; $I^2 = 0\%$; N=712), improved psoriasis by 1.3 points on a 6-point global improvement scale. Other very potent steroids (amcinonide, halcinonide and fluocinolone acetonide [with occlusion]) and potent steroids (betamethasone valerate, betamethasone-17, 21-dipropionate [plus salicylic acid]) were reported only in single trials with smaller patient numbers (and thus less precision) but with similar benefits.

The vitamin-D3 analogue calcipotriol demonstrated a modest benefit against placebo although findings were heterogeneous (2 trials; $I^2: 69.2\%$; N=457) with the only trial of significant size suggesting a 0.6 point improvement on a 6-point global improvement scale. Calcipotriol combined with betamethasone dipropionate suggested significant benefit against placebo but substantial heterogeneity (2 trials; $I^2 = 90\%$; N=854), with individual trials reporting 0.7 and 1.5 point gains on a 6-point scale.

Two further treatments, each assessed by one small trial, were no more effective than placebo (ciclopirox olamine shampoo, and salicylic acid).

Placebo-controlled trials do not provide adequately precise findings to rank all available treatment options using indirect (placebo-controlled) comparisons. However available evidence suggests a ranking of monotherapies for effectiveness of clobetasol propionate (very potent corticosteroid), betamethasone dipropionate (potent steroid) and then calcipotriol (vitamin-D3 analogue).

Head-to-head trials

Direct (head-to-head) comparisons were made of vitamin D analogues (alone or in combination) with other treatments (Figure 4). Twelve studies contributed data from 5413 patients. Trial durations ranged from 4 to 8 weeks in eleven studies, but the duration was 52 weeks in one trial.⁴⁸

FIGURE 4 HERE

Trials comparing vitamin D analogue monotherapy with very potent or potent steroid monotherapy consistently favoured corticosteroid treatment. One small trial comparing calcipotriol and clobetasol propionate supported the indirect comparison of these two treatments (SMD 0.37; 95% CI 0.05 to 0.69; N=151) with a 0.5 point gain on a 6-point global improvement scale favouring clobetasol propionate. Two trials comparing calcipotriol with betamethasone dipropionate (SMD 0.48; 95% CI 0.32 to 0.64; $I^2 = 60\%$, N=1676) and with betamethasone valerate (SMD 0.37; 95% CI 0.20 to 0.55; $I^2 = 0\%$, N=510) favoured corticosteroid treatment with 0.6 and 0.5 point gains respectively on a 6-point global improvement scale. We also pooled the trials comparing vitamin D analogues with potent or very potent steroids (SMD 0.45; 95% CI 0.36 to 0.53; $I^2 = 1\%$, N=2337). Thus corticosteroids provided approximately a 10% improvement in average scores compared with calcipotriol on a 6-point global improvement scale.

Combination therapy involving vitamin D analogue and corticosteroid offered a small advantage over corticosteroid alone (SMD -0.18; 95% CI -0.26 to -0.10; $I^2 = 0\%$, N=2444) of 0.2 points on a 6-point global improvement scale. Combination therapy involving vitamin D analogue and corticosteroid offered an improvement over calcipotriol alone, although findings were heterogeneous (4 trials; $I^2 = 82\%$, N=2581), with gains of 0.5 to 1.2 points on a 6-point global improvement scale.

Findings were heterogeneous for trials comparing calcipotriol with coal tar polytherapy (3 trials; $I^2 = 90\%$, $N=835$), ranging from no benefit to 1.2 points on a 6-point global improvement scale.

Withdrawals

For most treatments, rates of total withdrawal, withdrawal due to adverse events, withdrawal due to treatment failure were similar to those for placebo ('placebo-like') and not statistically significantly different; however, evidence for individual treatments was typically informed by individual small trials. When pooled findings from multiple trials were assessed, placebo-like withdrawal was only supported for calcipotriol (3 trials; $I^2=0\%$; $N=517$). Overall, evidence on clobetasol propionate suggested the withdrawal rate was similar to placebo but findings were heterogeneous (5 trials; $I^2=89\%$; $N=1006$). There was evidence from two trials that withdrawal rates for combined calcipotriol and betamethasone valerate was lower than placebo (RD -9%; 95%CI -16% to -3%; 2 trials; $I^2=0\%$; $N=854$).

Withdrawal rates for head-to-head comparisons of treatments consistently suggested slightly lower withdrawal from corticosteroids than from calcipotriol although this finding was not significant at the level of individual treatments. There was some evidence to suggest greater withdrawal with calcipotriol than combined calcipotriol and betamethasone valerate, although findings were heterogeneous (5 trials; $I^2=79\%$; $N=2847$), with higher withdrawal for calcipotriol varying from 5% to 18%.

Adverse events

Rates of local adverse events were very low and placebo-like, although only consistently informed by multiple trials and substantial numbers of patients for calcipotriol and clobetasol propionate.

Evidence from head-to-head trials supports the central finding of no important differences between treatments. Calcipotriol monotherapy, when compared with combined calcipotriol and

betamethasone, was associated with higher adverse event rates although some of these findings were heterogeneous.

Seven of the 19 trials that included a corticosteroid (alone or in combination) reported that atrophy had been assessed.^{33 40 46 50-52 57} Four trials reported no atrophy: treatments tested in these trials included clobetasol propionate shampoo,⁴⁰ potent corticosteroids,⁵⁰ and combination treatment with calcipotriol and betamethasone dipropionate.^{46 48} The remaining three trials reported instances of atrophy,^{33 51 52} all investigating clobetasol propionate. The method used to assess atrophy was described in only two trials and was unclear in all other trials. In Luger 2008,⁴⁸ a 52 week trial that compared combination therapy with vitamin D monotherapy, an independent adjudication committee decided whether the cases observed by the investigator were likely to be attributable to treatment. Poulin 2010 relied on self-report by study participants.⁵¹

Discussion

This review identified 26 trials of scalp psoriasis with 8,020 participants, with most trials investigating moderate to severe disease. Despite a range of topical therapeutic options there is substantial evidence for only a few treatment options: clobetasol propionate, betamethasone dipropionate, betamethasone valerate, calcipotriol and calcipotriol combined with potent steroid. Other corticosteroids suggest similar performance although findings are imprecise or based on findings of single trials. We did not find evidence to support the first-line use of a tar-based shampoo (with or without a keratolytic, such as salicylic acid, for significant scaling), a current formulary recommendation.⁵⁸

All treatments were more effective than placebo, meaning that all may have clinical value in the management of individual patients. Corticosteroids out-performed the vitamin D3 analogue calcipotriol: although indirect evidence from placebo-controlled trials favoured very potent above

potent steroids this was not apparent in head-to-head evidence with calcipotriol. However, we did not review very potent compared with potent steroid treatment directly. Combined treatment with vitamin D3 analogue and corticosteroid offered a small advantage over steroid alone and might be a treatment option in treatment resistant scalp psoriasis.

In overview, withdrawal and adverse event rates were very low in absolute terms, placebo-like and similar when comparing between treatments. There is some evidence that combined calcipotriol and betamethasone dipropionate is better tolerated than calcipotriol alone. Evidence presented in trials is insufficient to make any statement about corticosteroid-induced skin atrophy, and it is possible that cases of atrophy have gone unreported.

A limitation of the analysis is that with relatively few trials informing comparisons it was not possible to explore heterogeneous findings meaningfully. Heterogeneity may arise due to methodological or clinical diversity between trials. Trials were not often adequately reported so methodological variation cannot be excluded. Variations in age, gender, severity and ethnicity are examples of potential clinical diversity that may promote heterogeneous findings. For example Tying 2010⁵⁴ and Jemec 2008⁴¹ were both 8-week, double blind parallel group trials comparing combination therapy with its vehicle (placebo gel). Both trials found combination treatment to be significantly more effective than placebo (Figure 1), but the effect sizes were qualitatively different: -0.62 [-0.98, -0.27] and -1.28 [-1.48, -1.08]. In both trials, around 72% of patients on active treatment responded (very mild disease or clearance) but placebo response differed (41% vs. 23%). Tying 2010 recruited Hispanic, Latino, Black and African American patients, 63% male and none with mild disease. Jemec 2008 recruited predominantly white patients (96%), 45% male; 6.5% with mild disease, and 37.3% (vs. 19.8%) with severe or very severe disease. Thus there are multiple candidates for heterogeneous findings.

Conclusions

There is evidence for the effectiveness and tolerability of a range of topical therapeutic options for scalp psoriasis, although this evidence is adequate for a limited number of treatments. On effectiveness grounds, very potent (clobetasol propionate) or potent steroid treatments should be preferred to vitamin D3 analogue (calcipotriol). Calcipotriol combined with potent steroid may be a therapeutic option in cases that do not respond to monotherapy. The atrophic potential of corticosteroid treatments for scalp psoriasis remains unclear, and future studies should report cases of atrophy consistently and using robust assessment methods.

References

Table 1: Electronic databases searched

Database	Date searched
EMBASE	to 2011/02
MEDLINE	to 2011/02
Science Citation Index (SCI)	to 2011
Conference Proceedings Citation Index (CPCI-S)	to 2011
Biosis	to 2011
Dissertation Abstracts	all publication years
Inside Conferences	all publication years
CENTRAL Cochrane Library web interface	to 2011/02
Cochrane Skin Group's Trials Register	to 2011/02

Table 2: Outcome measures assessed in the review

Rank ^a	Primary Outcome measures	Construct
1	Investigator Assessment of Global Improvement; ^b or the equivalent static score, Investigator Global Assessment of Disease Severity	Improvement from baseline, usually scaled from worse to cleared; higher scores indicate greater improvement. Disease severity usually scaled from 'absence of disease' to 'very severe disease'; higher scores indicate more severe disease.
2	Total Severity Score	Redness (erythema), thickness (infiltration) and scaling (sometimes also itching (pruritis)) of target plaque(s). Scored separately then summed.
3	Psoriasis Area Severity Index (PASI) ^c	Redness, thickness, and scaliness of the lesions (each graded on a 0 to 4 scale), weighted by the area of involvement (0 to 6) and summed. Scored from 0 to 72.

4	* Patient (or Subject) Assessment of Global Improvement; ^b or the equivalent static score, Patient (or Subject) Global Assessment of Disease Severity	See <i>Investigator Assessment of Global Improvement</i>
^a Order for inclusion in 'combined endpoint' ^b Global improvement data are entered as a negative values, thus a reduction denotes a positive improvement for the active treatment consistent with other measures. ^c No study used the PASI score for scalp psoriasis		

Table 3: Descriptive statistics of the study characteristics

Number of studies	26
Number of participants	8,020
Trial sample size [mean, range]	308 [22, 1505]
Participant age [mean]	47.7 ^a
Participant gender [% male: mean]	46.6% ^b
Publication Year [range]	1978, 2010
Treatment duration [weeks] [mean, range]	7.5 [1.5, 52]
Follow-up duration [weeks] [mean, range]	10.8 [2, 52] ^c
Study design	
Both placebo and active comparisons	1
Head-to-head comparison only	11
Placebo comparison only	14
Between patient	25
Within patient	1
Method of randomisation	
Block randomisation	1
Computerised	7
Not reported	18
Concealment of treatment allocation	
Adequate	1
Unclear	25
Blinding	
Double blind	19
Single blind	2
Open	3
Not reported	2
Baseline comparability demonstrated	
Yes	19
Partial	2
Not reported / unclear	5

Note: summary statistics are based on data from 26 studies, with the following exceptions:
age ^a [N=19], gender ^b [N=21] and duration of follow up ^c [N=25].

Figure 1: Variation in participants' disease severity across the 26 trials of scalp psoriasis

Figure 2: Study quality, shown using the 'Risk of bias graph'

Note: review authors' judgements about each risk of bias item are presented as percentages across all included studies

Figure 3: Placebo-controlled trials of scalp psoriasis: treatment effectiveness

Figure 4: Active-controlled trials of scalp psoriasis: treatment effectiveness

1. Hellgren L. *Psoriasis. The prevalence in sex, age and occupational groups in total populations in Sweden: morphology, inheritance and association with other skin and rheumatic diseases.* Stockholm: Almqvist & Wiksell, 1967.
2. Krueger GG, Bergstresser PR, Lowe NJ, Voorhees JJ, Weinstein GD. Psoriasis. *Journal of the American Academy of Dermatology.* 1984;11(5 Pt 2):937-47.
3. Simons RD. Additional studies on psoriasis in the tropics and in the starvations camps. *J Invest Dermatol* 1949;12:285-294.
4. Yip SY. The prevalence of psoriasis in the Mongoloid race. *Journal of the American Academy of Dermatology.* 1984;10(6):965-8.
5. Griffiths CEM, Christophers E, Barker JNWN, Chalmers RJG, Chimenti S, Krueger GG, et al. A classification of psoriasis vulgaris according to phenotype. *British Journal of Dermatology* 2007;156(2):258-62.
6. van de Kerkhof PCM. Combinations and comparisons. *Clinics in Dermatology* 1997;15(5):831-4.
7. Gupta MA, Gupta AK, Watteel GN. Perceived deprivation of social touch in psoriasis is associated with greater psychologic morbidity: an index of the stigma experience in dermatologic disorders. *Cutis* 1998;61(6):339-42.
8. Finlay AY. Coping with psoriasis. *British Medical Journal* 1995;310(6995):1673.
9. Finlay AY. Psoriasis from the patient's point of view. *Archives of Dermatology.* 2001;137(3):352-3.
10. Finlay AY, Coles EC. The effect of severe psoriasis on the quality of life of 369 patients. *British Journal of Dermatology.* 1995;132(2):236-44.
11. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. *Clinical & Experimental Dermatology.* 1994;19(3):210-6.
12. McKenna SP, Cook SA, Whalley D, Doward LC, Richards HL, Griffiths CE, et al. Development of the PSORIQoL, a psoriasis-specific measure of quality of life designed for use in clinical practice and trials. *British Journal of Dermatology* 2003;149(2):323-31.
13. Ortonne JP. Psoriasis: Evaluation of quality of life. *Annales de Dermatologie et de Venereologie* 2000;127(Suppl. 2):2s19-2s22.
14. Richards HL, Fortune DG, Main CJ, Griffiths CE. Stigmatization and psoriasis. *British Journal of Dermatology* 2003;149(1):209-11.
15. Stern RS. Epidemiology of Psoriasis. *Dermatologic Clinics* 1995;13(4):717-722.

16. Chan CS, Van Voorhees AS, Lebwohl MG, Korman NJ, Young M, Bebo BF, Jr., et al. Treatment of severe scalp psoriasis: from the Medical Board of the National Psoriasis Foundation. *Journal of the American Academy of Dermatology* 2009;60(6):962-71.
17. Tagami H. Triggering factors. *Clinics in Dermatology* 1997;15(5):677-85.
18. Barker JN. The pathophysiology of psoriasis. *Lancet*. 1991;338(8761):227-30.
19. Griffiths CEM. The immunological basis of psoriasis. *Journal of the European Academy of Dermatology & Venereology* 2003;17(s2):1-5.
20. Stern RS. Psoriasis. *Lancet*. 1997;350(9074):349-53.
21. Griffiths CEM, Barker JNWN. Pathogenesis and clinical features of psoriasis. *Lancet* 2007;370(9583):263-71.
22. Tsoi LC, Spain SL, Knight J, Ellinghaus E, Stuart PE, Capon F, et al. Identification of 15 new psoriasis susceptibility loci highlights the role of innate immunity. *Nature Genetics* 2012;44(12):1341-8.
23. Papp K, Berth-Jones J, Kragballe K, Wozel G, de la Brassinne M. Scalp psoriasis: a review of current topical treatment options. *Journal of the European Academy of Dermatology & Venereology* 2007;21(9):1151-60.
24. Bottomley JM, Taylor RS, Rytto J. The effectiveness of two-compound formulation calcipotriol and betamethasone dipropionate gel in the treatment of moderately severe scalp psoriasis: A systematic review of direct and indirect evidence. *Current Medical Research and Opinion* 2011;27(1):251-268.
25. American Academy of Dermatology Work Group, Menter A, Korman NJ, Elmetts CA, Feldman SR, Gelfand JM, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 6. Guidelines of care for the treatment of psoriasis and psoriatic arthritis: case-based presentations and evidence-based conclusions. *Journal of the American Academy of Dermatology* 2011;65(1):137-74.
26. Mason AR, Mason J, Cork M, Dooley G, Edwards G. Topical treatments for chronic plaque psoriasis (protocol). *Cochrane Database of Systematic Reviews* 2004(1):CD005028.
27. Mason AR, Mason J, Cork M, Dooley G, Edwards G. Topical treatments for chronic plaque psoriasis. *Cochrane Database of Systematic Reviews* 2009(2):CD005028.
28. Mason AR, Mason J, Cork M, Dooley G, Hancock H. Topical treatments for chronic plaque psoriasis. *Cochrane Database of Systematic Reviews* 2013(3).
29. van de Kerkhof PCM. An Update on Vitamin D3 Analogues in the Treatment of Psoriasis. [Review] [70 Refs]. *Skin Pharmacology & Applied Skin Physiology* 1998;11(1):2-10.
30. Higgins J, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]*: The Cochrane Collaboration. Available from www.cochrane-handbook.org, 2011.
31. Barrett C, Lowson D, Blades KJ, investigators MI. Limited benefit of combined use of tar-based shampoo with 50 microg/ml calcipotriol solution in scalp psoriasis. *Journal of Dermatological Treatment* 2005;16(3):175.
32. 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(2):107-13.
33. Cook-Bolden FE, Goffe BS, Hudson CP, Sofen HL. Efficacy and safety results from a randomized, double-blind, vehicle-controlled study of clobetasol propionate spray for the treatment of moderate to severe plaque psoriasis of the scalp. *Journal of the American Academy of Dermatology* 2010;62(3 SUPPL. 1):AB140.
34. Duweb GA, Abuzariba O, Rahim M, al-Taweel M, Abdulla SA. Scalp psoriasis: topical calcipotriol 50 micrograms/g/ml solution vs. betamethasone valerate 1% lotion. *International Journal of Clinical Pharmacology Research* 2000;20(3-4):65-8.

35. Elie R, Durocher LP, Kavalec EC. Effect of Salicylic Acid on the Activity of Betamethasone-17,21-Dipropionate in the Treatment of Erythematous Squamous Dermatoses. *Journal of International Medical Research* 1983;11(2):108-12.
36. Ellis CN, Horwitz SN, Menter A. Amcinonide Lotion 0.1% in the Treatment of Patients with Psoriasis of the Scalp. *Current Therapeutic Research - Clinical and Experimental* 1988;44(2):315-324.
37. Franz TJ, Parsell DA, Halualani RM, Hannigan JF, Kalbach JP, Harkonen WS. Betamethasone valerate foam 0.12%: a novel vehicle with enhanced delivery and efficacy. *International Journal Of Dermatology* 1999;38(8):628-32.
38. Franz TJ, Parsell DA, Myers JA, Hannigan JF. Clobetasol propionate foam 0.05%: a novel vehicle with enhanced delivery. *International Journal Of Dermatology* 2000;39(7):535-8.
39. Green C, Ganpule M, Harris D, Kavanagh G, Kennedy C, Mallett R, et al. Comparative Effects of Calcipotriol (Mc903) Solution and Placebo (Vehicle of Mc903) in the Treatment of Psoriasis of the Scalp. *British Journal Of Dermatology* 1994;130(4):483-7.
40. Jarratt 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. *Journal of Drugs in Dermatology: JDD* 2004;3(4):367-73.
41. Jemec GBE, Ganslandt C, Ortonne J-P, 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. *Journal of the American Academy of Dermatology* 2008;59(3):455-63.
42. A Randomized, Double- Blind, Parallel Group, Dose-Ranging Comparison of the Efficacy and Safety of Calcipotriene Solution in the Treatment of Scalp Psoriasis. American Academy of Dermatology, 54th annual Meeting.; 1996 10th - 15th February.
43. Klaber MR, Hutchinson PE, Pedvis-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 (1 mg/ml) in the treatment of scalp psoriasis. *British Journal Of Dermatology* 1994;131(5):678-83.
44. Klaber MR, McKinnon C. Calcipotriol (DovonexR) scalp solution in the treatment of scalp psoriasis: Comparative efficacy with 1% coal tar/1% coconut oil/0.5% salicylic acid (CapasalR) shampoo, and long-term experience. *Journal Of Dermatological Treatment* 2000;11(1):21-28.
45. Köse O. Calcipotriol ointment vs clobetasol solution in scalp psoriasis. *Journal Of Dermatological Treatment* 1997;8:287.
46. 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. *British Journal of Dermatology* 2009;161(1):159-66.
47. Lepaw MI. Double-Blind Comparison of Halcinonide Solution and Placebo Control in Treatment of Psoriasis of the Scalp. *Cutis* 1978;21(4):571-3.
48. Luger TA, Cambazard F, Larsen FG, Bourcier M, Gupta G, Clonier F, et al. A Study of the Safety and Efficacy of Calcipotriol and Betamethasone Dipropionate Scalp Formulation in the Long-Term Management of Scalp Psoriasis. *Dermatology* 2008;217(4):321-328.
49. Olsen EA, Cram DL, Ellis CN, Hickman JG, Jacobson C, Jenkins EE, 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. *Journal of the American Academy of Dermatology* 1991;24(3):443-7.
50. Pauporte M, Maibach H, Lowe N, Pugliese M, Friedman DJ, Mendelsohn H, et al. Fluocinolone acetonide topical oil for scalp psoriasis. *Journal of Dermatological Treatment* 2004;15(6):360-364.

51. Poulin Y, Papp K, Bissonnette R, Guenther L, Tan J, Lynde C, et al. Clobetasol propionate shampoo 0.05% is efficacious and safe for long-term control of scalp psoriasis. *Cutis* 2010;85(1):43-50.
52. 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. *Journal of Dermatological Treatment* 2005;16(1):31-36.
53. Shuttleworth D, Galloway DB, Boorman GC, A.E. D. A double-blind, placebo-controlled study of the clinical efficacy of ciclopirox olamine (1.5%) shampoo for the control of scalp psoriasis. *Journal Of Dermatological Treatment* 1998;9(3):163-7.
54. Tying S, Mendoza N, Appell M, Bibby A, Foster R, Hamilton T, et al. A calcipotriene/betamethasone dipropionate two-compound scalp formulation in the treatment of scalp psoriasis in Hispanic/Latino and Black/African American patients: Results of the randomized, 8-week, double-blind phase of a clinical trial. *International Journal of Dermatology* 2010;49(11):1328-1333.
55. van de Kerkhof PCM, Green C, Hamberg KJ, Hutchinson PE, Jensen JK, Kidson P, et al. Safety and efficacy of combined high-dose treatment with calcipotriol ointment and solution in patients with psoriasis. *Dermatology* 2002;204(3):214-221.
56. 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. *British Journal of Dermatology* 2009;160(1):170-6.
57. Luger T, Kidson P, Cambazard F, Larsen FG. A 1-year, randomized, double-blind safety study of long-term treatment of a new gel formulation containing calcipotriene plus betamethasone dipropionate in scalp psoriasis. *Journal of the American Academy of Dermatology* 2008;58(2):AB134-AB134.
58. Joint Formulary Committee. *British National Formulary 64 (BNF 64). September 2012*. London: Pharmaceutical Press, 2012.