TITLE: Betamethasone for Adults with Scalp Psoriasis: A Review of the Clinical and Cost-Effectiveness

DATE: 30 March 2015

CONTEXT AND POLICY ISSUES

Psoriasis is a chronic skin disease resulting in raised papules and plaques that have thick silvery white scales.\(^1,2\) Approximately 2% of people have psoriasis, and the scalp is likely the most common area for psoriasis lesions, with up to 80% of people with psoriasis having scalp involvement.\(^3\) Scalp psoriasis can be more difficult to treat relative to other areas of the body due to the presence of hair on the scalp, resulting in patients having difficulty applying topical treatments.\(^2,3\) In addition, many patients find both the symptoms of scalp psoriasis itself, including itching, burning, and pain, and treatment distressing given the visibility of the scalp, and scalp psoriasis is associated with a reduced quality of life.\(^1,2\)

The visibility of the scalp and the reduced quality of life associated with scalp psoriasis highlight a need for treatments that are both effective and do not have a negative impact on appearance. Topical treatment options include corticosteroids such as betamethasone, coal tar, keratolytic agents such as salicylic acid, and vitamin D3 derivatives such as calcipotriol.\(^4\) Some vehicles in which these agents are formulated may be less likely to penetrate scalp lesions, as well as contribute to patients being embarrassed to apply the agents to the scalp, such as ointments and creams.\(^3\) The use of a foam vehicle has been offered as an alternative to other vehicles, which may better penetrate the scalp plaques and be more aesthetically pleasing for the patient. Betamethasone valerate 0.12% is available as a foam in Canada, indicated for “the relief of the inflammatory and pruritic manifestations of moderate to severe psoriasis of the scalp for up to 4 weeks in adult patients”.\(^5\)

The purpose of this Rapid Response report was to review the clinical effectiveness and cost-effectiveness of betamethasone foam compared with other formulations of betamethasone and calcipotriol for the treatment of scalp psoriasis.
RESEARCH QUESTIONS

1. What is the clinical effectiveness of betamethasone foam compared with other formulations for adults with scalp psoriasis?

2. What is the clinical effectiveness of betamethasone compared with calcipotriol for adults with scalp psoriasis?

3. What is the cost-effectiveness of betamethasone for adults with scalp psoriasis?

KEY FINDINGS

Betamethasone 0.12% foam was significantly more effective than betamethasone 0.1% lotion and standard treatment (including other corticosteroids and calcipotriol) for reducing psoriatic sum scores (including erythema, scaling, pruritus, and burning) after 28 days of treatment.

METHODS

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2015, Issue 3), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 1995 and March 2, 2015.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

<table>
<thead>
<tr>
<th>Table 1: Selection Criteria</th>
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<tbody>
<tr>
<td>Population</td>
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<td>Intervention</td>
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</table>
| Comparator                  | Q1. Betamethasone foam compared with other topical betamethasone formulations at a similar concentration  
Q2. Calcipotriol  
Q3. Betamethasone foam compared with other formulations or calcipotriol |
| Outcomes                    | Q1 and Q2: Clinical effectiveness  
Q2: Cost effectiveness |
| Study Designs                | Q1 and Q2: Health technology assessments, systematic review, meta-analyses, randomized controlled trials, non-randomized studies  
Q3: Economic evaluations |
Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to January 1, 1995.

Critical Appraisal of Individual Studies

The included randomized studies were critically appraised using the Cochrane Risk of Bias Tool. Summary assessments were not completed for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

SUMMARY OF EVIDENCE

Details of study characteristics, critical appraisal, and study findings are located in Appendices 2, 3, and 4, respectively.

Quantity of Research Available

A total of 407 citations were identified in the literature search. Following screening of titles and abstracts, 401 citations were excluded and six potentially relevant reports from the electronic search were retrieved for full-text review. A total of 16 potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 20 publications were excluded for various reasons, while two publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

Study Design

One of the included studies was a randomized, open-label, multicentre cross-over study, and was published in 2003. The other included study was a randomized, double-blind, multicentre study, and was published in 1999.

Country of Origin

One study originated from Italy, and the other study originated from the United States.

Patient Population

The Italian study included 241 people with moderate to severe scalp psoriasis, although no information was provided in terms of how this was determined. People were excluded from the study if they had a history of allergic dermatitis with corticosteroids or calcipotriol, were pregnant or breastfeeding, or had a history of non-response to topical treatments. In addition, use of immunosuppressive systemic treatments was not permitted during the study, and participants were instructed to not use other scalp therapies such as shampoos containing salicylic acid, coal tar, ketoconazole, or zinc pyrithione.

The study by Frantz and colleagues enrolled 190 patients with moderate to severe scalp psoriasis, defined as “involvement of at least 10% of the scalp and a minimum score of 2 (0 = none; 1 = mild; 2 = moderate; 3 = severe; 4 = very severe) for each of the primary signs of
Betamethasone for Scalp Psoriasis

Individuals who had used topical scalp therapies in the 2 weeks prior, or who had received systemic antipsoriatic therapy in the 4 weeks prior to the start of the study were excluded. All participants were required to use the same shampoo, and were not allowed to use any other scalp therapies during the study.

Interventions and Comparators

One study compared betamethasone valerate 0.12% foam with standard therapies, of which 55% received topical corticosteroids (among the 55% who received corticosteroids, 70% received mometasone, 25% received betamethasone dipropionate, 3% received betamethasone valerate, and 2% received hydrocortisone butyrate) and calcipotriol lotion (45% of participants in the standard therapy group received calcipotriol). Dosages of the agents were not described. Although this study did include betamethasone as an option, all individuals who received steroids were reported together, therefore it was not possible to assess the impact of individual corticosteroids compared with betamethasone foam. The other study compared betamethasone valerate 0.12% foam with placebo foam, betamethasone 0.1% lotion, and placebo lotion.

Outcomes

Both studies evaluated the change in scaling score, plaque thickness score, pruritus score, and erythema score, and the clinical global score obtained from adding the score from the individual items from baseline to 29 days, and baseline to 4 weeks. In addition, Andreassi and colleagues examined patient treatment acceptability and the influence of treatment on the Psoriasis Disability Index.

Summary of Critical Appraisal

Strengths of the study conducted by Andreassi and colleagues included the reporting of randomization sequence generation, blinding of study assessors evaluating efficacy, reporting of those who did not complete the study and how they were handled in the study analysis (those who did not complete the study were included in the analysis using last observation carried forward, and non-completers were even across groups), adequacy of the sample size calculation for the primary outcome, and the inclusion of appropriate outcomes. Limitations of the study included lack of reporting of how treatment allocation was concealed, and the use of a modified questionnaire to assess patient treatment acceptability. It was unclear whether the modified version of the questionnaire was previously validated. In addition, although participants were blinded to treatment by the use of identical packaging when the study medication was dispensed, since this was a cross-over study, the treatment vehicle likely would have been obvious to the patient. This would have had an impact on efficacy measures if the patient was preferentially less adherent to one of the treatments, as adherence to therapy was not measured.

In terms of generalizability, study investigators included individuals with moderate to severe scalp psoriasis, but did not define how this was determined. In addition, those with a history of non-response to topical therapies were excluded from the study, as were those using systemic immunosuppressive therapy to treat their scalp psoriasis.
A strength of the study conducted by Frantz and colleagues included the evaluation of appropriate effectiveness outcomes, although they did not consider patient acceptance or quality of life outcomes. This study had numerous limitations, however, including lack of reporting of how the randomization sequence was generated, no reporting of how treatment allocation was concealed or methods for blinding of participants or study investigators, no a priori sample size calculation, and losses to follow up without description of the reasons for withdrawing from the study. Also, there was no pre-defined primary outcome, and a number of statistical tests were performed, increasing the likelihood of a statistically significant result due to chance.

In terms of generalizability of the study results, individuals with moderate to severe scalp psoriasis were eligible for the study, and the criteria used to determine severity was clearly defined. Individuals who had received topical therapy in the past two weeks or systemic therapy in the past four weeks were excluded from the study.

Summary of Findings

Clinical effectiveness of betamethasone foam compared with other betamethasone formulations for adults with scalp psoriasis

One study compared betamethasone valerate foam 0.12% to betamethasone valerate 0.1% lotion, as well as placebo in both vehicles. Over the study duration of 28 days, betamethasone foam was found to significantly reduce scaling, plaque thickness, and erythema scores relative to betamethasone lotion, whereas there was no statistical difference found for pruritus score. Both agents were significantly better than placebo for reducing all psoriasis scores. In addition, both investigators and participants found that a greater proportion of people who received betamethasone foam (72% and 77%, respectively) reported being completely clear or almost clear of disease at the end of treatment, and this was significantly greater than those receiving betamethasone lotion (47% for both investigators and participants), placebo foam (21% for both investigators and participants) and placebo lotion (21% by investigators and 14% by participants).

Clinical effectiveness of betamethasone compared with calcipotriol for adults with scalp psoriasis

One study evaluated betamethasone foam compared to standard treatment, including calcipotriol. Betamethasone foam was found to significantly reduce the overall mean psoriasis sum score (which included erythema, scaling, pruritus, and burning) from baseline after a 4 week treatment period relative to standard treatment, which included corticosteroids and calcipotriol. When compared to calcipotriol alone, betamethasone foam was significantly more effective at reducing overall sum score after 4 weeks of therapy (P < 0.001). A greater proportion of participants who received betamethasone foam were deemed to be completely clear or almost clear of scalp psoriasis relative to participants who received standard treatment (88%; 95% confidence interval [CI]: 82% to 94% versus 66%; 95% CI: 58% to 74%). In addition, participants who received betamethasone foam consistently reported significantly better patient acceptance measures on the modified Finlay-Kahn questionnaire compared to those who received standard treatment, including improvement in appearance, impact on psychological problems, interference with work and hobbies, and cosmetic acceptability of the treatment.
Cost-effectiveness of betamethasone for adults with scalp psoriasis

No evidence was identified for this question.

Limitations

The studies included in this rapid report have a number of limitations. Each study examined patients for approximately 28 days, therefore it is unclear whether the efficacy of betamethasone foam is retained for a longer duration of therapy.\(^7,8\) The study comparing betamethasone foam to betamethasone lotion was associated with a number of limitations including unclear methods for blinding, no pre-defined primary outcome and associated sample size calculation, and unclear reporting of those lost to follow up, so bias may have impacted the study results, particularly if there was differential losses to follow up or if blinding methods were ineffective and study assessors were aware of the therapy the patient was receiving.\(^8\) In addition, the study comparing betamethasone foam to calcipotriol included patients receiving calcipotriol in a treatment group of patients receiving standard therapy. As a result, the analyses examining patients receiving calcipotriol only should be interpreted with caution because it is a subgroup analysis that was not pre-specified.\(^7\) Neither study evaluated adherence to therapy or adherence to restrictions on type of shampoo that could be used, therefore this may have impacted efficacy results.\(^7,8\) Lastly, no cost effectiveness studies were identified, therefore it is unclear whether the clinical benefits associated with betamethasone foam translate into cost-effectiveness for patients with scalp psoriasis.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Betamethasone 0.12% foam was found to be significantly more effective than betamethasone 0.1% lotion and standard treatment (including other corticosteroids and calcipotriol) for reducing psoriatic sum scores after approximately 28 days of treatment. In addition, betamethasone foam was rated consistently significantly better on patient acceptability questions relative to standard treatment. It is unclear whether the clinical benefit found with betamethasone foam would translate into cost-effectiveness of this agent relative to other agents.

PREPARED BY:
Canadian Agency for Drugs and Technologies in Health
Tel: 1-866-898-8439
www.cadth.ca
REFERENCES


APPENDIX 1: Selection of Included Studies

407 citations identified from electronic literature search and screened

401 citations excluded

6 potentially relevant articles retrieved for scrutiny (full text, if available)

16 potentially relevant reports retrieved from other sources (grey literature, hand search)

22 potentially relevant reports

20 reports excluded:
- irrelevant population (5)
- irrelevant intervention (9)
- irrelevant comparator (1)
- irrelevant outcomes (1)
- other (review articles, editorials) (4)

2 reports included in review
### Characteristics of Included Randomized Controlled Trials

<table>
<thead>
<tr>
<th>First Author, Publication Year, Country</th>
<th>Study Design</th>
<th>Patient Characteristics</th>
<th>Intervention(s)</th>
<th>Comparator(s)</th>
<th>Clinical Outcomes</th>
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</thead>
<tbody>
<tr>
<td>Andreassi, 2003, Italy</td>
<td>Randomized, cross-over (with at least 4 weeks washout period), open-label, multicentre</td>
<td>Adults with moderate to severe scalp psoriasis</td>
<td>n = 121 randomized to start with betamethasone valerate 0.12% foam applied twice daily</td>
<td>n = 121 randomized to start with standard therapy, as determined by dermatology clinic, applied once or twice daily depending on the agent</td>
<td>Primary outcome: clinical global score was calculated by adding the score for each item Assessment of a target lesion for scaling, itching, burning, and erythema on a five-point scale: 0 – completely cured 1 – mild 2 – moderate 3 – severe 4 – very severe Patient treatment acceptability and assessment of the influence of treatment on the Psoriasis Disability Index was assessed with a modified Finlay-Khan questionnaire The change in scores from baseline to 4 weeks was calculated for all assessments and compared between treatments</td>
</tr>
<tr>
<td>First Author, Publication Year, Country</td>
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<tr>
<td>Frantz, 1999, United States&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Randomized, double blind, multicentre</td>
<td>Adults with moderate to severe scalp psoriasis</td>
<td>n = 57 Betamethasone valerate 0.12% foam Applied twice daily for 28 consecutive days</td>
<td>n = 28 Placebo foam n = 58 Betamethasone valerate 0.1% lotion n = 29 Placebo lotion Applied twice daily for 28 consecutive days</td>
<td>Assessment of a target lesion for scaling, erythema, and plaque thickness on a seven-point scale: 0 – completely clear 1 – almost clear 2 – marked improvement 3 – moderate improvement 4 – slight improvement 5 – no change 6 – worse Pruritus assessed on a 0 – 4 scale: 0 – none 1 – mild 2 – moderate 3 – severe 4 – very severe The patient’s global assessment of response was calculated by evaluating the proportion of patients judged to be completely clear or almost clear of disease at the end of 28 days The change from baseline to 29 days was calculated for all assessments and compared between groups.</td>
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</tbody>
</table>
APPENDIX 3: Critical Appraisal of Included Publications

Strengths and Limitations of Randomized Controlled Trials using the Cochrane Risk of Bias Tool

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Andreassi, 2003</strong>&lt;sup&gt;7&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>• Sequence generation for randomization was performed using a computer-generated randomization program.</td>
<td>• Unclear how treatment allocation was performed.</td>
</tr>
<tr>
<td>• Blinding was performed by ensuring efficacy was evaluated by investigators who were unaware of the treatment allocation.</td>
<td>• Blinding unlikely to have been effective for patients given the study design (cross-over) and the obvious differences in vehicles of the products. This may have impacted patient adherence, which was not measured.</td>
</tr>
<tr>
<td>• 241 patients were randomized, and 210 completed treatment. Among these, 18 withdrew due to lack of efficacy (8 in the betamethasone group and 10 in the standard treatment group) and 13 did not attend study visits (7 in the betamethasone group and 6 in the standard treatment group). Authors stated they used last observation carried forward to analyze patients who did not complete the study.</td>
<td>• Unclear if the modified Finlay-Khan questionnaire used to assess patient treatment acceptability has been validated.</td>
</tr>
<tr>
<td>• Outcomes were clearly reported as they were described in the methods.</td>
<td>• Adherence to treatment and restrictions on other therapies such as shampoos were not evaluated.</td>
</tr>
<tr>
<td>• Sample size calculation was performed with appropriate estimates.</td>
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</table>

<p>| Frantz, 1999&lt;sup&gt;8&lt;/sup&gt; | | |
| • Efficacy outcomes were clearly reported as they were described in the methods. | • Sequence generation for randomization of participants was not described. |
| | • Method for treatment allocation was not described. |
| | • Although authors state that the study was double-blind, there was no description of the measures used to blind participants and investigators. |
| | • There was not a pre-defined primary outcome and a number of statistical tests were performed, increasing the risk for type 1 error. |
| | • There was no sample size calculation performed. |
| | • There were no quality of life outcomes |</p>
<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
</tr>
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</table>
|           | • A total of 190 individuals were randomized, and 172 completed the study. There was no description of whether there were differential losses to follow up in the treatment groups, reasons for why individuals did not complete the study, and individuals with missing data were excluded from the analysis.  
• Adherence to treatment and restrictions on other therapies such as shampoos were not evaluated. |
APPENDIX 4: Main Study Findings and Author’s Conclusions

<table>
<thead>
<tr>
<th>Summary of Findings of Included Studies</th>
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</thead>
<tbody>
<tr>
<td><strong>Main Study Findings</strong></td>
<td><strong>Author’s Conclusions</strong></td>
</tr>
<tr>
<td><strong>Andreassi, 2003</strong></td>
<td></td>
</tr>
<tr>
<td>Mean sum score:</td>
<td>The sum score at the end of the treatment phase was significantly lower relative to baseline for patients who received betamethasone foam relative to those who received standard treatment.</td>
</tr>
<tr>
<td>• Baseline: 7.6 (95% CI: 7.3 – 7.9)</td>
<td>• Betamethasone foam was also found to be more effective at reducing the baseline sum score than other steroids and calcipotriol when the standard treatment group was stratified into type of treatment.</td>
</tr>
<tr>
<td>• Betamethasone foam: 1.5 (95% CI: 1.3 – 1.7)</td>
<td>• Betamethasone was associated with a significant improvement in symptoms measured on the modified Finlay-Khan questionnaire compared with standard treatment, including itching, burning or pain, psychological problems, interference with work or hobbies, change in appearance, whether the treatment worked, whether relatives noticed an improvement in the participant’s scalp psoriasis, and whether the participant considered the current treatment acceptable.</td>
</tr>
<tr>
<td>• Standard treatment: 3.1 (95% CI: 2.8 – 3.4)</td>
<td>• “Clinical efficacy of BVM was superior (p &lt; 0.001) than both corticosteroids and calcipotriol when used at standard treatment.” – page 136</td>
</tr>
<tr>
<td>Investigator’s global assessment of efficacy – percentage of participants judged to be completely clear or almost clear at the end of treatment:</td>
<td>• “In conclusion, this new, low-residue, thermolabile foam formulation of betamethasone valerate has shown a superior clinical efficacy and patient acceptability in comparison with the standard available topical treatments for scalp psoriasis.” – page 137</td>
</tr>
<tr>
<td>• Betamethasone foam: 88% (95% CI: 82% – 94%)</td>
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<tr>
<td>• Standard treatment: 66% (58% - 74%)</td>
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| **Frantz, 1999**                        |                           |
| Mean change in scaling score from baseline to 29 days: | Participants in the betamethasone foam group demonstrated significantly greater improvement in all signs of |
| • Betamethasone foam: - 2.0             |                           |
### Summary of Findings of Included Studies

<table>
<thead>
<tr>
<th>Main Study Findings</th>
<th>Author’s Conclusions</th>
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</thead>
</table>
| • Betamethasone lotion: -1.5  
  • Placebo foam: -0.75  
  • Placebo lotion: -0.9 | psoriasis after 28 days of treatment compared to patients betamethasone lotion and placebo groups. |
| Mean change in plaque thickness score from baseline to 29 days: |
  • Betamethasone foam: -2.2  
  • Betamethasone lotion: -1.5  
  • Placebo foam: -0.6  
  • Placebo lotion: -0.6 | All comparisons between betamethasone foam and all other treatment groups were statistically significantly different except change in pruritus score (p = 0.1720) |
| Mean change in pruritus score from baseline to 29 days: |
  • Betamethasone foam: -1.9  
  • Betamethasone lotion: -1.6  
  • Placebo foam: -0.8  
  • Placebo lotion: -0.7 | Both participants and investigators found betamethasone foam to have the greatest percentage of individuals to be completely clear or almost clear at the end of the treatment phase, and this was significantly greater than betamethasone lotion, placebo foam, and placebo lotion. |
| Mean change in erythema from baseline to 29 days: |
  • Betamethasone foam: -1.6  
  • Betamethasone lotion: -1.25  
  • Placebo foam: -0.6  
  • Placebo lotion: -0.6 | “Data for 172 evaluable patients showed that those treated with BMV foam experienced significantly greater psoriatic improvement than patients treated with a currently marketed lotion product”. – page 632. |
| Investigator’s global assessment of efficacy – percentage of participants judged to be completely clear or almost clear at the end of treatment: |
  • Betamethasone foam: 72%  
  • Betamethasone lotion: 47%  
  • Placebo foam: 21%  
  • Placebo lotion: 21% | “When comparing the study formulations to other scalp psoriasis treatments that the patients had used, 68% of BMV foam treated patients gave the foam formulation the highest rating possible, compared to only 40% of the BMV lotion treated patients.” – page 632 |
| Participant’s global assessment of efficacy – percentage of participants judged to be completely clear or almost clear at the end of treatment: |
  • Betamethasone foam: 77%  
  • Betamethasone lotion: 47%  
  • Placebo foam: 21%  
  • Placebo lotion: 14% |

BMV: betamethasone valerate; CI: confidence interval

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*Betamethasone for Scalp Psoriasis*