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Is High Dose Intramuscular Alefacept a More Effective and Safe Treatment Option in Visibly Reducing the Severity of Chronic Plaque Psoriasis in Men and Women 16 Years and Older Compared to Standard IV and IM Treatment Forms?

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Is High Dose Intramuscular Alefacept a More Effective and Safe Treatment Option in Visibly Reducing the Severity of Chronic Plaque Psoriasis in Men and Women 16 Years and Older Compared to Standard IV and IM Treatment Forms?

Andrew Foster, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

December 16, 2011
Abstract

Objective: The objective of this selective EBM review is to determine whether or not high dose intramuscular alefacept is a more effective and a safe treatment option in visibly reducing the severity of chronic plaque psoriasis in men and women 16 years and older compared to standard IV and IM treatment forms.


Data Sources: Randomized, controlled clinical trials comparing alefacept to a control group were found using PubMed database.

Outcome Measured: Disease improvement and the adverse effect of headache. Disease improvement was measured using the Physician’s Global Assessment (0=clear, 5=severe) and the Psoriasis Area and Severity Index (0 = no disease, 72 = maximal disease). Numbers needed to treat were calculated for efficacy and numbers needed to harm was calculated to determine safety.

Results: The efficacy, based on NNT, of high dose alefacept, 30 mg IM was calculated based on Cafardi et al’s trial to be 8 compared to Krueger’s trial of 4, and Ortonne’s 5. NNH for headaches were calculated to be -8 for Cafardi et al, -100 from Krueger, and 34 from Ortonne.

Conclusion: After researching the three randomized control trials, alefacept 30 mg IM weekly for 12 weeks does not provide more effective results when treating chronic plaque psoriasis compared to standard doses of 7.5 mg IV or 15 mg IM weekly. Headaches were also seen more commonly as an adverse effect with high dose alefacept. As a result, standard doses of the biologic agent should be continued to be used to treat chronic plaque psoriasis that does not respond to other interventions and more studies must be further performed with alefacept 30 mg IM weekly.

Key Words: Chronic plaque psoriasis, alefacept, efficacy.
Introduction:

“Psoriasis is hyperproliferation of epidermal keratinocytes combined with inflammation of the epidermis and dermis. It affects about 1 to 5% of the population worldwide; light-skinned people are at greater risk. Peak onset is roughly bimodal, most often at ages 16 to 22 and at ages 57 to 60, but the disorder can occur at any age.1” The dermatologic disease is chronic and currently does not have a cure. The most common type is plaque psoriasis frequently found to appear on the extensor surfaces of body1. An estimated 2.5% Caucasians and 1.5% African Americans in the United States are affected.2 The estimated medical cost is 11.25 billion a year for United States to treat this condition.2 Approximately 60 percent of psoriasis patients missed an average of 26 days of work a year due to their illness2.

The cause of psoriasis is still unknown but there are suggestions. Currently, the disease is thought to be autoimmune with T cells being greatly involved in the rapid cell turnover rate. The unknown mechanism results in cells attacking the keratinocytes and causing an excessive growth rate. As a result, what is seen on the skin with plaque psoriasis is a silvery scale with an erythematous base that can be pruritic1.

There is an extensive list of treatments available to treat psoriasis and its subtypes. “Mild plaque psoriasis can be treated with emollients, keratolytics, tar, topical corticosteroids, vitamin D3 analogs, or anthralin alone or in combination. Exposure to sunlight is beneficial, but sunburn can induce exacerbations. Moderate to severe plaque psoriasis should be treated with topical agents and either phototherapy or systemic agents. Immunosuppressants are used for quick, short-term control (eg, in allowing a break from other modalities) and for the most severe disease. Immunomodulatory agents (biologics) are used for moderate to severe disease unresponsive to other agents.1”
This paper researches Alefacept, a biological agent that is fairly new and has been used both intramuscularly and intravenously to treat plaque psoriasis. Standard doses consist of 15 mg intramuscular (IM) and 7.5 mg intravenous (IV). 30 mg IM is a high dose that is thought to have more desired effects than the standard doses.

**Objective:**

The objective of this selective EBM review is to determine whether or not high dose intramuscular alefacept is a more effective and a safe treatment option in visibly reducing the severity of chronic plaque psoriasis in men and women 16 years and older compared to standard IV and IM treatment forms.

**Methods:**

Each study was dichotomous data involving men and women of various ages who were diagnosed with chronic plaque psoriasis for at least twelve months prior to the study. The biological agent alefacept was administered for 12 weeks in either 30 mg IM, 15 mg IM , or 7.5 mg IV bolus and compared with the control group. Each patient’s severity was determined by the Psoriasis Area and Severity Index (PASI) and Physician Global Assessment (PGA). PASI determines the severity with a scale ranging from 0 – 72. 72 means the severity is most severe and includes the entire body surface area (BSA). PGA measures how clear a person’s skin is. The scale ranges from 0 – 5 with 5 being severe psoriasis. The articles researched included two randomized double blind parallel group studies and one single center randomized open label study.

Cafardi et al compared 30 mg IM for 12 weeks to 30 mg IM for 6 weeks followed by 15 mg IM for 6 weeks. The safety, efficacy, and tolerability were assessed. Krueger compared 12 weeks of 7.5 mg IV over 30 seconds to a placebo group. Two courses were preformed making
the study 24 weeks long. This paper researches only one course which included weeks 1 – 12. Ortonne compares 15 mg IM to a placebo group. Ortonne initial time frame was 24 weeks but this paper researches only the initial 12 weeks. Ortonne and Krueger like Cafardi et al assessed the safety, efficacy, and tolerability.

Words used when searching were chronic plaque psoriasis, alefacept, and efficacy. Each article was published, peer reviewed, and printed in English. PubMed database was used to locate the three articles. Articles were selected based on relevance and patient oriented evidence that matters. Inclusion criteria had to meet at least 16 y.o with chronic stable plaque psoriasis, good health, with normal CD4$^+$ counts, and BSA of at least 10% effected. Exclusions included other forms of psoriasis other than plaque, serious systemic infections within 3 months, HIV positive, hepatitis, malignancies, treatment with phototherapy, steroids, etc within 4 weeks. Table 1 below provides specific inclusion and exclusion criteria for each article. P-value, absolute benefit increase (ABI), relative benefit increase (RBI), numbers needed to treat (NNT), and absolute risk increase (ARI), relative risk increase (RRI), and numbers needed to harm (NNH) were evaluated. These values were specifically looked at to determine which intervention provided the most effective treatment with the least adverse effects.
## Demographics and Characteristics of included studies (Table 1)

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th># patients</th>
<th>Age</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>W/D</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cafardi 2008</td>
<td>RCT</td>
<td>16</td>
<td>32-60</td>
<td>Men and women at least 19 y.o. with a hx or chronic plaque psoriasis requiring treatment. Were in good health and normal CD4 counts.</td>
<td>Known hepatitis, TB, HIV, CD4 &lt;380, hx of malignancy, known immunosuppression on other than DM, local infx within 3 months. Other txt within 28 days, pregnant, planning to become pregnant, nursing mothers.</td>
<td>2</td>
<td>30 mg IM once a week Alefacept for 12 wks.</td>
</tr>
<tr>
<td>Kruger 2003</td>
<td>RCT</td>
<td>183</td>
<td>&gt; or equal to 16</td>
<td>At least 16 y.o. chronic stable plaque psoriasis more than 12 months with BSA 10%, CD4 wnl,</td>
<td>Any other form of psoriasis, local or systemic infx within 3 months, HIV, hepatitis, malignancy, other forms of systemic tx within 4 weeks or topical within 2 weeks except on scalp, palms, groin, arm folds region or soles.</td>
<td>15</td>
<td>7.5 mg IV bolus for 30 seconds once a week Alefacept for 12 weeks.</td>
</tr>
<tr>
<td>Ortonne 2003</td>
<td>RCT</td>
<td>166</td>
<td>18-84</td>
<td>At least 18 y.o. with chronic stable plaque psoriasis for at least 12 months, BSA of at least 10% and CD4 count wnl.</td>
<td>Other forms of psoriasis, HIV, hepatitis, systemic infx within 3 months, malignancy, systemic tx within 4 weeks or topical tx within 2 weeks except for scalp. groin, arm folds, palms, and soles.</td>
<td>N/A</td>
<td>15 mg Alefacept IM once a week for 12 weeks.</td>
</tr>
</tbody>
</table>
Results:

Cafardi et al researched a 12 week course of 30 mg alefacept IM and compared the results to a 6 week course of 30 mg IM followed by 15 mg for an additional 6 weeks. Fifty percent of the patients responded with a PASI reduction of 50 – 75% with the 30 mg dose for 12 weeks compared to a 37.5% PASI reduction in the control group. Eight patients were initially given a PGA score of 3 and after intervention 3 continued to have a PGA score of 3. This is compared to the control in which 5 patients initially had a PGA score of 3 and after treatment 2 patients continued to have a score of 3. The ABI was calculated to be 0.125 and the RBI was 0.333. Numbers needed to treat was calculated to be 8. Results are displayed in Table 2.

Krueger’s study involved a two course consisting of a total of 24 weeks. This paper researches only course 1, the initial 12 weeks of 7.5 mg IV alefacept compared to IV placebo. 56% of the patients in the experiment group saw over a 50% PASI reduction compared to a 23% reduction in the placebo group. The results were significant with a p-value <0.001. Course 1 PGA score of clear or almost clear was seen in 23% of course 1 experiment patients compared to 6% of placebo group. The ABI was calculated to 0.320 and the RBI was 1.33. Numbers needed to treat was found to be 4.

Ortonne’s study includes 12 weeks of dosing and 12 weeks of follow up. This paper researches the initial 12 weeks of dosing. 15 mg IM alefacept was compared to a placebo group. 57% responded to a greater than 50% PASI reduction compared to the 35% in the control. The results were significant, p-value 0.002. The PGA of clear or almost clear was seen 22% of the experiment group compared to 8% in the control. The ABI was calculated to be 0.220 and RBI was 0.630. The NNT was determined to be 5.
Table 2: Results of therapeutic intervention PASI

<table>
<thead>
<tr>
<th>Study</th>
<th>Experiment</th>
<th>Control</th>
<th>P-value</th>
<th>ABI</th>
<th>RBI</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cafardi</td>
<td>4/8</td>
<td>3/8</td>
<td>N/A</td>
<td>0.125</td>
<td>0.333</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>50.0%</td>
<td>38.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Krueger</td>
<td>205/367</td>
<td>43/186</td>
<td>&lt;0.001</td>
<td>0.320</td>
<td>1.33</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>56.0%</td>
<td>23.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ortonne</td>
<td>94/166</td>
<td>58/168</td>
<td>0.002</td>
<td>0.220</td>
<td>0.630</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>57.0%</td>
<td>35.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Result of therapeutic intervention PGA

<table>
<thead>
<tr>
<th>Study</th>
<th>Experiment</th>
<th>Control</th>
<th>P-value</th>
<th>ABI</th>
<th>RBI</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cafardi</td>
<td>0.25</td>
<td>0.25</td>
<td>0.01</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Krueger</td>
<td>0.23</td>
<td>0.06</td>
<td>N/A</td>
<td>0.17</td>
<td>2.83</td>
<td>6</td>
</tr>
<tr>
<td>Ortonne</td>
<td>0.22</td>
<td>0.08</td>
<td>&lt;0.001</td>
<td>0.14</td>
<td>1.75</td>
<td>8</td>
</tr>
</tbody>
</table>

Table 4 provides the results for numbers needed to harm. Headache was chosen because among the three trials the occurrence was common. Cafardi et al NNH was 8, for Krueger’s study 100 was calculated, and Ortonne’s study found -34 to be calculated.

Table 4: Results of adverse effects headaches.

<table>
<thead>
<tr>
<th>Study</th>
<th>Experiment</th>
<th>Control</th>
<th>P-value</th>
<th>ARI</th>
<th>RRI</th>
<th>NNH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cafardi et al</td>
<td>2/8</td>
<td>3/8</td>
<td>N/A</td>
<td>-0.130</td>
<td>-0.330</td>
<td>-8</td>
</tr>
<tr>
<td></td>
<td>25.0%</td>
<td>38.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Krueger</td>
<td>30/154</td>
<td>38/186</td>
<td>N/A</td>
<td>-0.010</td>
<td>-0.0500</td>
<td>-100</td>
</tr>
<tr>
<td></td>
<td>19.0%</td>
<td>20.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ortonne</td>
<td>30/166</td>
<td>26/168</td>
<td>N/A</td>
<td>0.030</td>
<td>0.200</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>18.0%</td>
<td>15.0%</td>
<td></td>
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</tr>
</tbody>
</table>

Discussion:

The results of the three randomized control trials suggests high dose alefacept weekly for 12 weeks was not as effective in treating chronic plaque psoriasis as compared to standard doses. Standard doses consisting of 15 mg IM and 7.5 mg IV had similar efficacy results with intravenous route allowing less patients needed to be treated to provide a PASI reduction of at least 50%. 
Analyzing the common adverse effect of headache in each of the control trials found intravenous administration of 7.5 mg alefacept provided the least amount of headaches. One hundred patients would have to be treated before one patient complained of the headaches. High dose alefacept was found to cause headaches the most.

The inclusion and exclusion criteria between the three studies were similar. Differences between trials included, Krueger allowing patients as young as sixteen while Cafardi et all set a minimum of nineteen. The number of patients 16 years old was not discussed in Kueger’s article. Another difference was Kueger and Ortonne set a boundary that subjects had to have stable plaque psoriasis with a diagnosis of at least 12 months while Cafardi et al only said the subjects had to have a history of chronic plaque psoriasis. Krueger and Ortonne had clear placebo groups in their study while Cafardi et al had a control group that consisted of two distinct treatments over the same time period. A major difference between these studies is the sample size. Cafardi et al had a sample size of 16 compared to 183 in Krueger’s study and 166 in Ortonne’s study.

**Conclusion:**

According to this EBM review, 30 mg alefacept IM once weekly does not provide more efficacy and safety when treating chronic plaque psoriasis as compared to standard doses. Greater number of patients were needed to treat to provide effective results and less patients were needed to cause adverse effects.

For the future, suggestions to improve studies looking at using high dose alefacept would be to use multiple centers to provide a greater range of results in order to have a larger sample size. Comparing a sample of 8 to 166 seems in effective. The other control trials used multicenters to conduct their research and collect data. Also, high dose alefacept should be
tested against a placebo and not another control group that does consist partially of the
experimental dose in it. This way all three trials are being tested against a control and would
make results each variable more consistent.
References


