H.P. Acthar Gel and Cosyntropin Review
Clinical and Financial Implications

Jacob Gettig, PharmD, MPH, BCPS; Joseph P. Cummings, PhD; and Karl Matuszewski, MS, PharmD

OVERVIEW

H.P. Acthar Gel Repository Injection (Questcor Pharmaceuticals) is a 39-amino-acid peptide natural form of adrenocorticotropic hormone (ACTH). It works by stimulating the adrenal cortex to secrete cortisol, corticosterone, aldosterone, and a few other weakly androgenic substances. In the body, corticotropin-releasing hormone (CRH) from the hypothalamus stimulates the release of ACTH from the anterior pituitary gland. Conversely, high levels of cortisol in the serum act via a negative biofeedback mechanism to decrease the output of ACTH.

The FDA has specifically labeled H.P. Acthar Gel for use in diagnostic testing of adrenal function. The package insert lists a variety of other diseases and disorders for which it may be used but stresses that patients should preferably be treated with corticosteroids. Examples of diseases for which ACTH may be used are acute multiple sclerosis (MS) exacerbations, rheumatoid arthritis, acquired hemolytic anemia, allergic conjunctivitis, palliative management of adult leukemia or lymphoma, and ulcerative colitis. Table 1 provides a complete listing.

Cosyntropin (Cortrosyn, Amphastar), a synthetic form of ACTH, is created by isolating the first 24 amino acids from the 39-amino-acid ACTH peptide. In countries outside the U.S., cosyntropin is sometimes called tetracosactide, but the two are the same chemically. A dose of cosyntropin 0.25 mg, similar to a dose of 25 units of ACTH, stimulates the adrenal cortex.

Prior to February 2008, cosyntropin was available only as the brand-name agent Cortrosyn. In February 2008, the FDA approved a cosyntropin solution for injection, and Sandoz launched the product in March 2008. The only FDA-labeled indication for cosyntropin is in diagnostic testing of adrenal function. A depot formulation of cosyntropin (Synacthen Depot) is not approved by the FDA in the U.S.; it is available only through a compassionate-use program through the specialty pharmacy Caligor Rx in New York, N.Y.

Cosyntropin products have also been used in an off-label fashion to treat a variety of diseases, including MS and infantile spasms. Unlike ACTH, which can be given intramuscularly or subcutaneously, Cortrosyn should be given only intramuscularly or intravenously; cosyntropin should be given only intravenously.

In May 2007, the FDA issued a non-approvable letter for H.P. Acthar Gel in treating infantile spasms. As a result, Questcor promised to work closely with the FDA to resolve the perceived deficits of its supplemental New Drug Application (sNDA). On August 27, 2007, Questcor announced a new strategy and business model for H.P. Acthar Gel Repository Injection. The cost of the product was increased from an average wholesale price (AWP) of $2,062.79 per vial to an estimated $23,000 per vial (see Table 2, page 252). The company explained that its price increase was crucial in order to continue manufacturing and distributing this agent to patients who needed it and to fund projects that could contribute to the company’s growth. Questcor estimated that a course of treatment for infantile spasm with H.P. Acthar Gel could approach costs of $80,000 to $100,000, which are in range with those for other rare diseases. This increase in price has led clinicians to question the therapeutic value of H.P. Acthar Gel, especially as it compares with lower-priced and potentially therapeutically equivalent alternatives such as cosyntropin and corticosteroids.

MAJOR CLINICAL USES

Although there are numerous possible uses of ACTH, this article focuses on the three most common indications: adrenocortical testing, MS, and infantile spasms (West syndrome).

Adrenal insufficiency. Arriving at the correct diagnosis is imperative; untreated, adrenal insufficiency can result in death. Primary adrenal insufficiency (Addison’s disease) is less prevalent than secondary adrenal insufficiency, which is usually caused by inappropriate use of corticosteroids; however, it can also result from the long-term appropriate use of corticosteroids. The prevalence of primary adrenal insufficiency is approximately 0.01%, whereas the estimated prevalence of secondary adrenal insufficiency is 50% or greater in patients using corticosteroids for long periods of time and at 30% in patients with pituitary dysfunction or in those who have undergone pituitary surgery.

Multiple sclerosis. MS is an autoimmune disease in which the body destroys its own myelin on nerve fibers. It afflicts about 400,000 people in the U.S. and 2.5 million people worldwide. There are four main MS presentations, characterized by whether the disease presents as progressive worsening or acute worsening, also known as relapses or exacerbations. About 85% of patients have the relapsing–remitting course, in which function deteriorates rapidly but then stabilizes; this occurs in a repeating pattern. Less rare are the other courses, which include primary–progressive, secondary–progressive, and progressive–relapsing MS.

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Dr. Gettig is Assistant Professor of Pharmacy Practice at Midwestern University–Chicago College of Pharmacy in Downers Grove, Illinois. Dr. Cummings is Senior Research Specialist in Technology Assessment at the University HealthSystem Consortium in Oak Brook, Illinois. Dr. Matuszewski is Vice President of Gold Standard in Tampa, Florida.

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West syndrome. This rare epileptic disorder consists of three main characteristics: infantile spasms, mental retardation, and hypsarrhythmia, a specific abnormal pattern. Hypsarrhythmia is detected by an electroencephalogram (EEG) and is characterized by slow waves of high voltage and random pattern of spikes that vary in duration and location. About 90% of cases are diagnosed during an infant’s first year of life.

The prevalence of West syndrome is low (0.015–0.02% in children 10 years of age and younger), but it is associated with a poor prognosis for normal mental development. Even though 90% of children are free of spasms by five years of age, 50% of them continue to experience a form of seizure disorder.

Benefits of ACTH. ACTH may have some advantages over other available agents for each of these conditions. Because ACTH was originally approved by the FDA in 1952, an impressive amount of safety and efficacy data is available. ACTH was one of the first drugs used to treat MS relapses with consistent success; in current practice however, corticosteroids, such as methylprednisolone, seem to be preferable over using ACTH in treating relapses in patients with MS. ACTH is supported in practice guidelines coauthored by the American Academy of Neurology and the Child Neurology Society, and it is considered “probably effective” for the short-term treatment of infantile spasms, which is the most strongly stated recommendation in the guidelines. Although vigabatrin (Sabril, Ovation Pharmaceuticals) is not available in the U.S., other countries, such as the United Kingdom, recommend it as the preferred agent for treating infantile spasms. Vigabatrin is a synthetic form of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter that is sometimes

Table 1  FDA-Approved Indications for H.P. Acthar Gel

<table>
<thead>
<tr>
<th>Disorder or Disease</th>
<th>Usage or Indication</th>
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<tbody>
<tr>
<td>Adrenal insufficiency</td>
<td>Diagnostic testing of adrenocortical function</td>
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<tr>
<td>Endocrine disorders</td>
<td>Nonsuppurative thyroiditis; hypercalcemia associated with cancer</td>
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<tr>
<td>Nervous system diseases</td>
<td>Acute exacerbations of multiple sclerosis</td>
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<tr>
<td>Rheumatic disorders</td>
<td>For short-term adjunctive therapy in acute episodes or exacerbations in psoriatic arthritis; rheumatoid arthritis, including juvenile rheumatoid arthritis; ankylosing spondylitis; acute and subacute bursitis; acute nonspecific tenosynovitis; acute gouty arthritis; post-traumatic arthritis; synovitis of osteoarthritis; epicondylitis</td>
</tr>
<tr>
<td>Collagen diseases</td>
<td>During an exacerbation or as maintenance therapy in selected cases of systemic lupus erythematosus; systemic dermatomyositis (polymyositis); acute rheumatic carditis</td>
</tr>
<tr>
<td>Dermatological diseases</td>
<td>Pemphigus; bullous dermatitis herpetiformis; severe erythema multiforme (Stevens–Johnson syndrome); exfoliative dermatitis; severe psoriasis; severe seborrheic dermatitis; mycosis fungoides.</td>
</tr>
<tr>
<td>Allergic states</td>
<td>Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment: seasonal or perennial allergic rhinitis; bronchial asthma; contact dermatitis; atopic dermatitis; serum sickness.</td>
</tr>
<tr>
<td>Ophthalmic diseases</td>
<td>Severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as allergic conjunctivitis; keratitis; herpes zoster ophthalmicus; iritis and iridocyclitis; diffuse posterior uveitis and choroiditis; optic neuritis; sympathetic ophthalmia; anterior segment inflammation; allergic corneal marginal ulcers</td>
</tr>
<tr>
<td>Respiratory diseases</td>
<td>Symptomatic sarcoidosis; Loeffler’s syndrome not manageable by other means; berylliosis; fulminating or disseminated pulmonary tuberculosis when used concurrently with antituberculous chemotherapy; aspiration pneumonia</td>
</tr>
<tr>
<td>Hematological disorders</td>
<td>Acquired (autoimmune) hemolytic anemia; secondary thrombocytopenia in adults; erythroblastopenia (red blood cell anemia); congenital (erythroid) hypoplastic anemia</td>
</tr>
<tr>
<td>Neoplastic diseases</td>
<td>For palliative management of leukemias and lymphomas in adults; acute leukemia of childhood</td>
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<tr>
<td>Edematous state</td>
<td>To induce a diuresis or a remission of proteinuria in the nephrotic syndrome without uremia of the idiopathic type or that caused by lupus erythematosus</td>
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<tr>
<td>Gastrointestinal diseases</td>
<td>To tide the patient over during a critical period of the disease in ulcerative colitis; regional enteritis</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy; trichinosis with neurological or myocardial involvement</td>
</tr>
</tbody>
</table>

Data from package insert, Questcor.1
deficient in patients with certain types of epilepsy. Vigabatrin works by mimicking the effects of GABA, thereby decreasing seizure frequency.19

Disadvantages of ACTH. When ACTH is compared with other agents, its most striking characteristic is its high price. At almost $30,000 per vial, its cost far exceeds that of any of the other alternatives that we describe.20 Table 2 summarizes differences in costs between ACTH and cosyntropin products. Other potential disadvantages in relation to comparable diagnostic and treatment options are discussed in the next section.

CURRENT PRACTICE AND ALTERNATIVES

Even before Questcor’s price increase in August 2007, the use of ACTH was limited. A 2007 survey of 50 University HealthSystem Consortium hospitals revealed that each facility used an average of 10 vials of ACTH annually and that 25% of this use was in ambulatory clinics. Given the current pricing for H.P. Acthar Gel, the average use of 10 vials per year would cost a hospital approximately $270,000 more than before August 2007.

Adrenal insufficiency. Cosyntropin may be preferred over ACTH in diagnosing adrenal insufficiency. Besides the obvious cost advantage, the cosyntropin test takes significantly less time (30 to 60 minutes); by contrast, an overnight wait is required for the ACTH test.1–3 Cosyntropin may also be less immunogenic than ACTH; amino acids 22 to 39 in ACTH seem to produce most of the molecule’s antigenicity.2 Thus, the cleaving of most of these amino acids from cosyntropin may render it less likely to elicit an allergic response.

Exacerbations of multiple sclerosis. The role of ACTH in treating MS exacerbations is also diminishing. ACTH has been replaced by high-potency corticosteroids because of their comparable, if not greater, effectiveness.21 ACTH does not improve MS exacerbations through any pathway but through stimulating corticosteroid production. Although the mechanism by which corticosteroids allay MS exacerbations is not well understood, it is thought that steroids reduce edema in the demyelinated area of nerve fibers, induce apoptosis of mature lymphocytes, and restore the blood–brain barrier.22 High-potency corticosteroids have become the standard of therapy for MS exacerbations.23 Doses of methylprednisolone range from 500 to 1,000 mg/day intravenously for three to seven days, followed by a tapering dose of oral prednisone 60 mg for 10 to 21 days.24

The long-term use of corticosteroids is not recommended because of potentially serious adverse effects such as osteoporosis, cataracts, hypothalamic–pituitary–adrenal axis (HPA) suppression, and psychosis. Plasma exchange has been used as a last line of treatment for MS exacerbations if high-dose corticosteroid therapy fails, but it has not been consistently effective.22

Infantile spasms. The use of ACTH in infantile spasms is not easily dismissed. Practice guidelines, reviews, and a meta-analysis support its use,13,14,17,25 and many of these sources cite ACTH as the first-line treatment choice.13,17,26 These sources generally agree that:

1. ACTH appears to be as effective as, if not more effective than, other therapies for the short-term cessation of infantile spasms.14,17,25
2. ACTH appears to be as effective as, if not more effective than, other therapies for the short-term termination of hypsarrhythmia.14,17,25
3. The effect of ACTH on long-term developmental outcomes in patients with infantile spasms warrants further research.13,14,17,25
4. The preferred dose and duration of treatment of infantile spasms with ACTH cannot be determined from the available evidence.14,17

Additional data. Several points are worth noting:

1. Some of the less-well-designed and more poorly reported studies do not explicitly distinguish between ACTH and cosyntropin; it cannot be determined whether the study patients received natural or synthetic ACTH.
2. Because some countries (e.g., Japan) do not have ready access to ACTH, cosyntropin is used interchangeably with ACTH.27
3. Some countries (e.g., the United Kingdom) advocate the use of vigabatrin (CPP-109, Catalyst) as a first-line therapy for infantile syndrome.19 Although vigabatrin is not commercially available in the U.S., it is in phase II trials and is being studied in cocaine and methamphetamine addiction.28,29

SUMMARY OF CLINICAL EVIDENCE

Because the literature on the wide variety of indications for ACTH dates back to the 1950s, we found it necessary to develop a systematic way of selecting studies to review. As explained previously, the use of ACTH in the diagnosis of adrenal insufficiency and in the treatment of MS exacerbations is decreasing. Therefore, our summary details the results of a Cochrane Systematic Review in the treatment of infantile spasms as well as prospective clinical trials involving 20 or more patients who used ACTH, cosyntropin, or both and an active comparator (e.g., prednisone, prednisolone, vigaba-

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Table 2: Costs of ACTH-Related Products

<table>
<thead>
<tr>
<th>Drug Product</th>
<th>Average Wholesale Price</th>
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<tbody>
<tr>
<td>H.P. Acthar Gel before August 27, 2007</td>
<td>$2,062.79 per vial of 80 units/ml, 5 mL (Red Book, 2007)</td>
</tr>
<tr>
<td>H.P. Acthar Gel as of July 2008</td>
<td>$29,086.25 per vial of 80 units/ml, 5 mL (Red Book, 2008)</td>
</tr>
<tr>
<td>Cortrosyn lyophilized powder</td>
<td>$106.58 per vial of 0.25 mg (Amphastar internal information), 10 vials per package</td>
</tr>
<tr>
<td>Cosyntropin solution for injection</td>
<td>$119.91 per vial of 0.25 mg (Sandoz internal information), 10 vials per package</td>
</tr>
</tbody>
</table>

Data from Questcor, May 2007;6 and National Institute for Clinical Excellence (NICE), April 2004.8
PATIENT SELECTION CRITERIA

Table 3 summarizes the studies included in the meta-analysis along with two additional studies by Lux et al.28,31

A phase 2 trial of several medications (carbamazepine, ACTH, nitrazepam, pyridoxine, and valproic acid) and surgery for the treatment of infantile spasms has been completed.34 In this trial, patients first received pyridoxine before other treatments; ACTH was second in the sequence of medications used. The study was sponsored by the National Center for Research Resources and the National Institute for Neurological Disorders and Stroke.38 Ongoing research involving ACTH and cosyntropin in the treatment of trauma and shock patients was also found at ClinicalTrials.gov.39

PATIENT SELECTION CRITERIA

The following excerpt from the package insert outlines the use of ACTH with respect to corticosteroids:

H.P. Acthar® Gel has limited therapeutic value in those conditions responsive to corticosteroid therapy; in such cases, corticosteroid therapy is considered to be the treatment of choice.1 Given this statement and the wide difference in price between corticosteroids and H.P. Acthar Gel, steroids can be used initially for many of the conditions for which ACTH is effective. An example of this stepwise approach is the treatment of MS exacerbations, for which corticosteroids are now preferred over ACTH; however, ACTH, which was formerly a primary therapy for MS exacerbations, may be tried if patients do not respond to corticosteroids.16

In diagnosing adrenal insufficiency, cosyntropin and ACTH are interchangeable and both carry an FDA-approved indication.1,2 In fact, cosyntropin is recommended in guidelines from 200844 and is often preferred over ACTH for reasons previously mentioned.

Although no direct comparisons have been made with cosyntropin and ACTH for patients with infantile spasms, some of the most rigorous studies performed to date28,31 have demonstrated positive clinical outcomes with cosyntropin compared with vigabatrin. A small study has suggested that low doses of cosyntropin might be just as effective as high doses for this condition.32 These results mirror those of another trial that compared high-dose and low-dose regimens of ACTH with similar success.35

FUTURE DEVELOPMENTS

When the FDA denied the indication of infantile spasms for Questcor’s H.P. Acthar Gel, the company said that it would work closely with the FDA to generate the necessary data to move forward on this indication. In December 2008, Questcor resubmitted an sNDA for this indication.45 To date, no decision by the FDA concerning the sNDA has been made public. The future market success of H.P. Acthar Gel is difficult to project and will largely depend on the successful FDA approval of the indication for infantile spasms.

CONCLUSION

The use of ACTH in the diagnosis of adrenal insufficiency and in the treatment of MS exacerbations is diminishing, with cosyntropin and corticosteroids, respectively, preferred over ACTH for these uses.

In prospective, randomized trials of ACTH or cosyntropin for the treatment of infantile spasms, between 40% and 90% of patients experienced cessation of spasms. Hypsarrhythmia, as diagnosed by EEG, resolved in 20% to 90% of patients, and relapse rates range from 14% to 33%.26 A more recent, larger, and better-designed study suggests that cessation of spasms with hormonal treatment (without distinguishing between prednisolone and cosyntropin) is likely to occur in 73% of patients.20 According to the best available evidence, hormonal treatment (without distinguishing between prednisolone and cosyntropin) does not appear to produce significantly different developmental outcomes than vigabatrin at 14 months of follow-up. Vigabatrin has been studied extensively for patients with infantile spasms and is recommended as a first-line treatment in the United Kingdom.19 It is not available in the U.S., but phase 2 trials are underway to assess its effects on cocaine and methamphetamine addiction.30,31

The cost of H.P. Acthar Gel increased dramatically in August 2007.3 In most situations, ACTH should be reserved for...
### Table 3 Prospective Comparative Clinical Trials of ACTH or Cosyntropin in Infantile Spasms

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of ACTH Used</th>
<th>No. of Patients*</th>
<th>Methodology</th>
<th>Results and Conclusions</th>
</tr>
</thead>
</table>
| Lux et al., 2005 | Cosyntropin/tetracosactide | 107             | • Randomized, open-label, multicenter study  
• Hormone† (n = 55) vs. vigabatrin (n = 52)  
• Median age = 14 months  
• Primary outcome measure = development at 14 months as measured by the VABS  
• Secondary outcome measure = presence of seizures and ADRs  
• Follow-up = 14 months | Results: VABS scores between hormone and vigabatrin treatment did not differ significantly (78.6 vs. 77.5, respectively; \( P = 0.73 \)). The proportion of infants who were seizure-free at the end of the study period was similar between groups (hormone, 22/55 [40%]; vigabatrin, 19/52 [37%]; \( P = 0.71 \)). In a subgroup analysis, mean VABS scores were significantly higher in patients with no known etiology of infantile spasms in the hormone group (88.2) compared with the vigabatrin (78.9) group (\( P = 0.025 \)).  
Conclusion: Treatment of infantile spasms with hormone or vigabatrin appears to produce similar developmental outcomes and cessation of spasms at 14 months. Hormonal treatment may result in better developmental outcomes than vigabatrin in patients with an unknown cause of infantile spasms, but further research is warranted. |
| Lux et al., 2004 | Cosyntropin/tetracosactide | 107             | • Stratified randomization, open-label, multicenter study  
• Prednisolone (n = 30) vs. tetracosactide (n = 25) vs. vigabatrin (n = 55), for analysis of prednisolone and tetracosactide grouped into hormone treatment arm (n = 55)  
• Median age = 6 months (range, 4–9 months)  
• Primary outcome measure = number of patients spasm-free at 13–14 days after randomization  
• Secondary outcome measure = number of spasm-free consecutive days before day 14; number of patients without hypsarrhythmia  
• Follow-up = 14 days | Results: Forty patients were free of spasms at 14 days. Significantly more patients were spasm-free at 14 days in the hormone group (prednisolone, 21; tetracosactide, 19; vigabatrin, 19/52 = 73%) than in the vigabatrin group (28/52 = 54%) (\( P = 0.043 \)). Significant differences in consecutive spasm-free days before day 14 were also detected (hormonal treatment, median days = 9; vigabatrin treatment, median days = 2.5; \( P = 0.038 \)). Hypsarrhythmia resolved in significantly more patients in the hormone group (81%) than in the vigabatrin group (56%) (\( P = 0.024 \)).  
Conclusion: At 14 days, hormonal treatment might be more effective than vigabatrin for stopping infantile spasms and hypsarrhythmia; however, given the small number of patients, it is difficult to draw conclusions about the comparative efficacy of prednisolone and tetracosactide. |
| Yanaguki et al., 1999 | Cosyntropin/tetracosactide | 26              | • Randomized, open-label study  
• High-dose cosyntropin (n = 13) vs. low-dose cosyntropin (n = 12)  
• High-dose (0.025 mg/kg per day) and low-dose cosyntropin (0.05 mg/kg per day) were given daily for 2 weeks and tapered to discontinuation in the following 2 weeks  
• Mean age = 34.5 weeks  
• Primary outcome measure = response to treatment (cessation of spasms and hypsarrhythmia on EEG)  
• Secondary outcome measures = long-term seizure and developmental status; ADRs  
• Follow-up = 4 weeks; 17 responders were followed for 1 year or more | Results: Response to treatment did not differ significantly between the high dose (11/13 = 85%) and the low dose (9/12 = 75%) (\( P > 0.05 \)). Long-term developmental outcomes and the presence of seizures at 1 year or more of follow-up did not differ between groups; however, the detailed methods of the follow-up protocol were not stated, so the quality of follow-up results might be suspect. Brain shrinkage, as measured by CT, and sleepiness in the first week of treatment were significantly more pronounced in the high-dose group (\( P < 0.05 \)).  
Conclusion: Patients taking high-dose or low-dose cosyntropin appear to have similar short-term responses to treatment. A low-dose cosyntropin regimen might be more tolerable than a high-dose regimen. |
<table>
<thead>
<tr>
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<th>Type of ACTH Used</th>
<th>No. of Patients*</th>
<th>Methodology</th>
<th>Results and Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vigevano et al., 1997</td>
<td>ACTH</td>
<td>42</td>
<td>• Randomized, open-label, response-mediated crossover study</td>
<td>Results: For the separate phases of the study, there was no difference in cessation of spasms with ACTH or vigabatrin, but a significant difference was detected when total response to treatment (phase 1 responders + phase 2 responders) was compared between ACTH (25 responders/35) and vigabatrin (13 responders/28) ($P = 0.007$). In general, more ACTH patients than vigabatrin patients experienced ADRs. Conclusion: ACTH and vigabatrin may result in similar rates of cessation of infantile spasms, but patients who initially do not respond to vigabatrin and who are switched to ACTH are more likely to experience cessation of spasms than the converse. Vigabatrin may be better tolerated than ACTH.</td>
</tr>
<tr>
<td>Baram et al., 1996</td>
<td>ACTH</td>
<td>29</td>
<td>• Randomized, single-blind study</td>
<td>Results: Patients receiving ACTH responded to treatment (clinical and EEG response) significantly more often than those receiving prednisone (13/15 [86.6%] vs. 4/14 [28.6%], respectively; $P = 0.002$). Patients were observed beyond 2 weeks, but the study was confounded by the fact that many patients originally receiving prednisone were switched to ACTH. However, most patients (25/29) still had abnormal results at their last follow-up visit (range, 2–48 months). Conclusion: The likelihood of clinical and EEG resolution of infantile spasms appears greater with ACTH than with prednisone; however, it is difficult to make conclusions about differences in long-term outcomes because the study was not designed to detect such differences.</td>
</tr>
<tr>
<td>Hrachovy et al., 1994</td>
<td>ACTH</td>
<td>59</td>
<td>• Randomized, blinded study</td>
<td>Results: The difference in response to treatment between high and low-dose ACTH was not statistically significant (50% and 58%, respectively). There was also no statistical difference in relapse between the two groups (15% and 21%, respectively). Hypertension occurred more frequently in the high-dose group than in the low-dose group (31% and 4%, respectively; $P = 0.025$). Conclusion: Patients with infantile spasms appear to respond at similar rates to high-dose and low-dose regimens of ACTH; however, high-dose ACTH patients may experience hypertension more frequently than low-dose ACTH patients.</td>
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</table>

*Methodology details and results for each study are provided in the table.*
patients who have not responded to treatment or who cannot tolerate corticosteroids and cosyntropin.

REFERENCES