Pilot study of monthly pulse adrenocorticotropic hormone (ACTH) or methylprednisolone as an add-on therapy to beta-interferons for long-term treatment of multiple sclerosis

Regina Berkovich, MD, PhD; Lylana Amezcua, MD; Dawood Subhani, MBBS; Steven Cen, PhD
University of Southern California, Keck School of Medicine, Department of Neurology; Los Angeles, CA, USA

ABSTRACT
Objective: The single-center, examiner-blinded pilot study evaluated the efficacy and safety of pulse adrenocorticotropic hormone (ACTH) treatment added to beta-interferon in breakthrough multiple sclerosis (MS) compared with pulse intravenous methylprednisolone (IVMP).

Background: ACTH may have immune-modulating mechanisms beyond adrenocortical suppression that are relevant to the MS disease course. Although ACTH gel is approved to treat MS relapses, its use as pulse therapy is less known.

Methods: MS patients receiving ongoing beta-interferon treatment were eligible if they had Expanded Disability Status Scale (EDSS) scores of 0.5-6.0 and relapsed at least once the previous year. Patients were randomly assigned to open-label ACTH (80 units IM once/day x 3 consecutive days) or IVMP (1 g x 1 dose) monthly for 12 months, with assessments every 3 months for 15 months. Outcomes included relapse rate (primary) and EDSS, MS Functional Composite, and MS Quality of Life scores.

Results: The study included 23 patients (ACTH, n=11; mean SD EDSS 4.6±1.5; IVMP, n=12; mean SD EDSS 4.6±1.3). Over 15 months, the cumulative rate of relapses/patient/month was 0.55 (95% CI: 0.12-2.6) in the ACTH (0 episodes; P=0.03) group and 2.6 (95% CI: 0.1-5.3) in the IVMP group. The cumulative rate of relapses/patient/month was greater in the IVMP group than the ACTH group (P=0.03). Patients in the ACTH group had statistically significantly stronger (P<0.001) improvement in Mental Health Inventory compared with the IVMP group (0.01±0.05 points/month vs 0.01±0.04 points/month; P=0.03).

Conclusions: These data suggest a potential benefit of ACTH pulse therapy compared with IVMP with more favorable safety profiles and psychiatric side effect profiles. Further studies, including additional randomized controlled trials, are needed to validate these findings.

INTRODUCTION

Inflammation, immunodegeneration, and animal and human data contribute to the morbidity and disease progression in multiple sclerosis (MS).1 Although several effective disease-modifying treatments are available for long-term MS management, breakthrough disease and progressive demyelination in MS remain a clinical challenge. Data to guide treatment decisions, particularly for breakthrough MS, are limited.

Monthly intramuscular methylprednisolone (IVMP) pulse therapy is commonly used in the treatment of breakthrough MS to ameliorate disease-modifying therapies; however, it is not always effective or well tolerated. Common adverse reactions, both short and long term, include corticosteroid-induced diabetes, hypertension, gastritis, and gastrointestinal ulcer, weight gain, edema, and psychological side effects. Additionally, regular administration of corticosteroids may suppress hypothalamic-pituitary-adrenal (HPA) axis function.2

Adrenocorticotropic hormone (ACTH) gel (H.P. Acthar® Gel, repository corticotropin injection; Questcor Pharmaceuticals, Inc., Hayward, CA) is a long-acting form of the full sequence ACTH (1-24) (80 units IM) that may include other pro-opiomelanocortin peptides, has been approved by the US Food and Drug Administration for treatment of MS relapses.3 However, ACTH pulse therapy for MS has not been evaluated in clinical trials.

Although the mechanism of action of ACTH has long been considered to be due to stimulation of cortical release, accumulating preclinical evidence suggests that ACTH also has corticosteroid-independent (extra-adrenal) direct effects on the immune and cytokine systems (CNS), which may be relevant to MS and other neuro-inflammatory conditions.4 5

- Extra-adrenal anti-inflammatory effects involve the suppressive effects of melanocortins, including ACTH, on the cellular level (i.e., as autocrine and paracrine regulators of the immune system; CNS-mediated pathway) through stimulation of all 5 melanocortin receptors.4 6 7
- ACTH and other melanocortins inhibit activation of nuclear factor B (NF-B), which leads to inhibition of production of a wide range of inflammatory mediators.8 9 10 extra-adrenal anti-inflammatory effects play a role in the extracellular cholinergic pathways and may have neuroprotective effects in spinal cord injury and protective effects in ischemic brain injury.10

These immune regulatory and direct, anti-inflammatory effects suggest that ACTH may be useful when given as pulse therapy for breakthrough MS.

This study evaluated pulse therapy with ACTH gel as an add-on therapy to beta-interferon.

METHODS

This was a single-center, randomized, examiner-blinded pilot study (July 2011–April 2012).

Patients
Inclusion criteria
- Adult MS patients (aged 18-45 years) receiving ongoing beta-interferon treatment (Avonex®, Betaseron®, or Rebif®) for at least 6 months
- Expanded Disability Status Scale (EDSS) scores of 0.5-6.0
- Able to perform neurological examinations were blinded to treatment group.
- The cumulative rate of relapses/patient/month was greater in the IVMP group than the ACTH group (P=0.03). Patients in the ACTH group had statistically significantly stronger (P<0.001) improvement in Mental Health Inventory compared with the IVMP group (0.01±0.05 points/month vs 0.01±0.04 points/month; P=0.03).

Conclusions: These data suggest a potential benefit of ACTH pulse therapy compared with IVMP with more favorable safety profiles and psychiatric side effect profiles. Further studies, including additional randomized controlled trials, are needed to validate these findings.

DISCLOSURES
- This study was supported through an investigator-initiated study by Questcor Pharmaceuticals, Inc.
- Regina Berkovich has served on advisory boards for Acorda, Avonex, Bayer, Biogen Idec, Genzyme, Teva, and Tianren and has received research funding from Questcor Pharmaceuticals, Inc. and additional financial or material support from Biogen Idec and Genzyme. She has been involved in investigator-initiated studies from National MS Society, Questcor and Tima.
- Laura Amezcua has served on advisory boards for Acorda, Bayer, Biogen Idec, Genzyme, Teva, and has been involved in investigator-initiated studies from California Neurological Society, Questcor and Tima.
- Dawood Subhani has served on advisory boards for Biogen Idec, Genzyme, Teva, and has been involved in investigator-initiated studies from National MS Society, Questcor and Tima.
- Steven Cen has served as a consultant for Acorda, Bayer, Biogen Idec, Genzyme, and Teva.
- All authors have no other disclosures.

REFERENCES
9. Stadelmann C. Adrenocorticotropic hormone (ACTH) gel (H.P. Acthar® Gel) provides significant improvement in Mental Health Inventory compared with intravenous methylprednisolone in patients with relapsing-remitting multiple sclerosis. J Neuroimmunol. 2010;220(1-2):81.
10. Sisoff M. Adrenocorticotropic hormone (ACTH) gel (H.P. Acthar® Gel) provides significant improvement in Mental Health Inventory compared with intravenous methylprednisolone in patients with relapsing-remitting multiple sclerosis. J Neuroimmunol. 2010;220(1-2):81.
11. Myhr KM, Mellgren SI. Adrenocorticotropic hormone (ACTH) gel (H.P. Acthar® Gel) provides significant improvement in Mental Health Inventory compared with intravenous methylprednisolone in patients with relapsing-remitting multiple sclerosis. J Neuroimmunol. 2010;220(1-2):81.