Pharmacodynamics and Tolerability of Repository Corticotropin Injection in Healthy Human Subjects: A Comparison With Intravenous Methylprednisolone

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Abstract

Repository corticotropin injection (porcine adrenocorticotropic hormone [ACTH] analog) and intravenous methylprednisolone (IVMP) are used to treat inflammatory conditions such as multiple sclerosis (MS) exacerbations and rheumatoid arthritis. This multiple-dose, randomized, crossover, open-label study evaluated and compared pharmacodynamic outcomes in subjects who received ACTH analog (80 U subcutaneously) or IVMP (1 g) daily for 5 days. Specific outcome measures included IVMP and cortisol concentrations, total cortisol-equivalent exposure, immune cell population changes, and tolerability. IVMP and ACTH analog increased granulocyte numbers and decreased lymphocyte counts; effects on both were significantly less pronounced with ACTH analog. Based on total cortisol-equivalent exposure (assuming linearity), administration of 80 U of ACTH analog equates to 30 mg IVMP. Because IVMP doses significantly higher than 30 mg are usually required to treat MS exacerbations, the lower cortisol-equivalent exposure of 80 U ACTH analog supports the hypothesis that efficacy of ACTH analog results from both steroid-dependent and -independent properties. Adverse events were mild in severity; subject incidence for adverse-event reporting was similar following both regimens. The clinical relevance of these findings in autoimmune disease populations is unknown and requires further evaluation.

Keywords

clinical pharmacology, pharmacodynamics, biomarkers, clinical research, pharmacology

Repository corticotropin injection (adrenocorticotropic hormone [ACTH] analog) is a highly purified sterile preparation of a porcine ACTH analog formulated in a repository gel for prolonged release after subcutaneous or intramuscular administration. ACTH analog is approved in the United States for the treatment of numerous autoimmune and inflammatory disorders, including rheumatoid arthritis, systemic lupus erythematosus, polymyositis, dermatomyositis, and exacerbations of acute multiple sclerosis (MS). The activity of ACTH analog was historically believed to result solely from its ability to stimulate adrenal corticosteroids, thereby indirectly modulating a variety of anti-inflammatory processes. The steroidogenic properties of ACTH result from activation of a G-protein-coupled receptor (known as melanocortin receptor-2; MC2R) expressed in adrenocortical cells. More recently, it has been demonstrated that MC2R is a member of a melanocortin receptor family (MC1–5R) expressed in multiple extra-adrenal tissues and cells. Nonclinical evidence suggests a potential role for melanocortin peptides, including ACTH, on inflammation and the immune response in both the peripheral and central nervous system that may be independent of endogenous cortisol production, as ACTH analog exhibits agonist binding at all 5 known melanocortin receptors (data on file, RD-010-00, Mallinckrodt Pharmaceuticals). Therefore, these data suggest that the mechanism of action of ACTH analog may result from anti-inflammatory and immunomodulatory properties in addition to its effects on endogenous steroidogenesis.

Because many of the clinical disorders treated with ACTH analog may also be managed with exogenous corticosteroids, the current study was performed to compare the pharmacodynamic (PD) effects of ACTH

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analog with those of intravenous methylprednisolone (IVMP).

Methylprednisolone is a synthetic corticosteroid that is administered orally or intravenously and is approved for a number of indications. Similar to other administered glucocorticoids, methylprednisolone works through cytoplasmic glucocorticoid receptors and does not bind to melanocortin receptors (data on file, RD-010-00, Mallinckrodt Pharmaceuticals). The doses of ACTH analog and IVMP evaluated in the current investigation may be used for the treatment of MS exacerbations, and both agents have demonstrated efficacy for this indication. However, a comparative study of key PD effects such as total steroid equivalency has not been performed. Such an evaluation could inform about differences in the mechanisms of action of the 2 drugs.

Thus, the objective of this study was to evaluate the total cortisol-equivalent exposure, effects on circulating immune cell populations (T cells, B cells, and select subpopulations), and tolerability of ACTH analog and IVMP in healthy human subjects. The doses of IVMP 1 g given intravenously and ACTH analog 80 U given subcutaneously were chosen on the basis that these are the most commonly administered doses of both medications used for the treatment of MS exacerbations.

Methods
The Bio-Kinetic Clinical Applications institutional review board reviewed and approved the study protocol. Subjects provided written informed consent for participation. The study was conducted in compliance with good clinical practice and the Declaration of Helsinki (2008).

Study Design
The study was a multiple-dose, randomized, open-label, crossover study of ACTH analog (H.P. Acthar Gel; Mallinckrodt Pharmaceuticals, St. Louis, Missouri) and IVMP (Solu-Medrol; Pfizer, New York, New York) in healthy subjects. To compare PD responses at doses relevant to clinical practice, ACTH analog and IVMP were administered at doses typically used to manage exacerbations of MS or other autoimmune disorders for which ACTH analog might be used clinically.

ACTH analog was administered as 80-U subcutaneous injections, and IVMP as 1.0-g intravenous infusions for 30 minutes, both daily for 5 days. All doses were given at a fixed and similar time each morning. Subjects were to abstain from all food and drinks (except water) for at least 8 hours prior to blood draws for safety laboratory assessments when fasting was required. During confinement, standardized meals were served during treatment days.

The 2 treatment arms consisted of 9 subjects each, who were randomized to ACTH analog or IVMP for the first period and then crossed over to the other treatment for the second study period following a 30-day washout period. The 30-day washout period was deemed more than sufficient and with no carryover effect, based on the short half-lives for cortisol and methylprednisolone.

Subjects were in-clinic from day -2 (2 days before dosing) to 48 hours post–day 5 dosing (day 7) for each dosing. Baseline was obtained (day -1) and follow-up visits occurred for each study period as outlined above.

Subjects
Eligible subjects included healthy, nonsmoking men and women between 18 and 50 years of age with a body mass index between 18.5 and 30 kg/m². Female subjects were of nonchildbearing potential or had agreed to use protocol-outlined acceptable forms of nonhormonal birth control. Exclusion criteria included evidence of any clinically significant disease; a history of disorders or surgical procedures that could interfere with the absorption, distribution, metabolism, and excretion of drugs; use of an investigational drug within 30 days before dosing; any history of long QT syndrome; and use of glucocorticoids (oral, inhaled, or topical) or any prescription or over-the-counter drug in the past 30 days, or any immunosuppressive agent for 3 months. Subjects were to have no known or suspected contraindications to ACTH analog or corticosteroids and no active infection or febrile illness. Subjects were also required to have a hemoglobin A1c value of <6.5%.

PD Assessments
Serum Cortisol. Blood for serum cortisol measurements was collected at the following times for the IVMP and ACTH analog arms: predose (0) and 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours postdose. Serum cortisol concentration was measured in samples collected at the same times before (day -1) and after IVMP (days 1, 3, and 5) and ACTH (days 1 and 5) administration. For IVMP, a day 3 measurement was made because a typical intravenous pulse corticosteroid regimen may be shorter than 5 days.

IVMP. Following IVMP treatment, blood for serum methylprednisolone measurements was collected at the following times: predose (0) and 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours postdose on days -1, 1, 3, and 5. Validated sensitive and specific liquid chromatography–mass spectrometry/mass spectrometry analyses were performed according to good laboratory practice guidelines.

Total Cortisol-Equivalent Exposure. As methylprednisolone is a corticosteroid with systemic action similar to but more potent than cortisol itself, the total cortisol-equivalent exposure from both endogenous cortisol and methylprednisolone was estimated and compared with the stimulatory effect of ACTH on cortisol release. For methylprednisolone, a conversion of 5 times was assumed, as methylprednisolone is considered to be 5 times more potent than cortisol (ie, every 1 mg of...
methylprednisolone = 5 mg of hydrocortisone or cortisol based on potency). The summary of data manipulation is as follows:

1. Methylprednisolone concentrations were converted to cortisol equivalent by multiplying the concentration data by 5.
2. Total concentration (C_total) was calculated by adding cortisol concentration and methylprednisolone concentration in cortisol equivalent following IVMP treatment.
3. C_total for baseline day -1 and on days 1 and 5 following ACTH analog treatment only included cortisol concentrations.

Flow Cytometry. Blood for flow cytometry analysis was collected at the following times in each arm of each study period: predose (0) and 1, 2, 4, 8, 12, and 24 hours postdose. A total of 4 subjects for each treatment arm, the same individuals in each study period, were randomized for these additional PD analyses. Samples were collected on days -1 (baseline), 1, 3, and 5 before and after IVMP administration, and on days -1 (baseline), 1, and 5 before and after ACTH analog administration. The following measurements were taken using flow cytometry: total lymphocytes, total B cells (naive B cells and plasma B cells), total T cells (T helper [Th] cells and T cytotoxic cells), and total granulocytes (neutrophils).

Other Safety Measurements
Blood glucose was monitored by a simple finger-stick test every day. Diastolic blood pressure (DBP) and systolic blood pressure (SBP) were measured. In addition, mean arterial pressure (MAP) was calculated using the following equation: MAP = ([2 × DBP + SBP]/3. These measurements were taken over 24 hours at baseline (on day -1) and on dosing days 1, 3, and 5 of each study period. They were obtained at the following times: 0, 0.25, 0.5, 2, 3, 4, 6, 8, 12, and 24 hours. For each study period, the predose (0) time on day 1 was defined as the baseline 24-hour time on day -1. The 24-hour vital signs for days 1, 3, and 5 were collected as predose on days 2, 4, and 6 of each study period.

Calculation of PD and Safety Parameters
The area under the effect curve (AUEC) for serum cortisol, serum cortisol-equivalent effect exposure, blood pressure (DBP, SBP, and MAP), and cell counts for flow cytometry were calculated on days -1, 1, 3, and 5 for IVMP and on days -1, 1, and 5 for ACTH analog. For all PD markers, parameters were baseline adjusted, with baseline corresponding to time-matched values obtained on day -1. Baseline adjustment was subject and period specific. Changes from baseline in individual blood glucose concentrations and flow cytometry counts were also calculated.

Safety Assessments
Safety measurements included the incidence and severity of adverse events (AEs); changes from baseline in laboratory measurements, electrocardiograms (ECGs), and vital signs; and changes in physical examination.

Statistical Analyses
A sample size of 9 subjects per group was chosen. No statistical hypothesis was proposed. Although the sample size for this clinical pharmacology study was not based on formal statistical power calculations, the sample size was consistent with safety, pharmacokinetic (PK), and PD evaluations performed for this type of exploratory clinical pharmacology study.

For serum cortisol, serum cortisol-equivalent exposure, blood glucose, blood pressure, and the different cell counts obtained by flow cytometry, the change-from-baseline AUEC after ACTH analog and IVMP administration was compared using a repeated-measures analysis of variance (ANOVA). The analysis was performed on PD parameters on their original scale (untransformed) and also after natural log (ln) transformation. The model included fixed effects for cohort, treatment (ACTH analog and IVMP), period (periods 1 and 2), and day (days 1, 3, and 5 for cortisol, flow cytometry cell counts, and blood pressure; days 1 through 5 for glucose), along with day-by-treatment interaction. Subject nested within cohort was to be included as a random effect. Day was specified as a repeated variable for each subject within a cohort. Each ANOVA was to include calculation of treatment and day-by-treatment interaction least-squares (LS) means, the difference between LS means, corresponding 90% confidence interval, and the P values of the difference. Additional multivariate analyses were performed to evaluate potential effects for body mass index (BMI) and sex on cortisol-equivalent exposure (change from baseline) AUEC. The parameters used in all analyses were tested for normality. If the data did not appear to be normally distributed, a nonparametric analysis was used on the untransformed data.

Statistical analysis was performed using PROC MIXED (SAS, Cary, North Carolina).

Results
Study Population
The demographic characteristics of the 18 subjects are shown in Table 1. For personal reasons, 1 subject did not return for period 2 after having received ACTH analog in period 1. The early termination was not deemed related to the drug. For this subject, data from period 1 were
included in appropriate analyses. Another subject was lost to follow-up but had sufficient data collected in periods 1 and 2 to be included in all analyses.

Cortisol
All subjects had measurable baseline endogenous serum cortisol concentrations on day -1. Mean serum cortisol concentrations following ACTH analog administration were higher than those observed following IVMP administration. Mean serum cortisol concentrations increased from baseline following a single dose of ACTH analog on day 1 and returned to baseline levels by 24 hours postdose (Figure 1). A similar but more pronounced increase was observed following multiple-dose administration on day 5. Mean serum cortisol concentrations following IVMP administration were generally lower than baseline on days 1 and 5 (Figure 1). Levels of serum cortisol were at endogenous levels on day -1 of period 2 and similar to the levels on day -1 of period 1, indicating no carryover effects in period 2.

IVMP Serum Concentrations
Figure 1A shows the mean (standard error of the mean) concentration–time profiles of methylprednisolone on days 1, 3, and 5. Concentrations were similar on days 1, 3, and 5. The half-life of methylprednisolone is 2.5 hours.19 Methylprednisolone levels were close to or below the limit of quantitation after a 28-day washout period in period 2, indicating no carryover effect in period 2.

Serum Cortisol-Equivalent Exposure
Peak and total cortisol-equivalent exposure, as measured by mean (arithmetic and geometric) total serum cortisol-equivalent AUEC, increased from baseline (day -1) following single-dose administration of ACTH analog on day 1 and following multiple-dose administration on day 5 (Table 2). AUEC was significantly higher following IVMP compared with ACTH analog dosing ($P < .001$; Table 2, Figure 2). This difference in serum cortisol-equivalent exposure translates an 80-U ACTH analog dose to approximately 30 mg (3% of 1 g) of IVMP. There

| Table 1. Demographic Characteristics |
|-------------------------------------|
| Characteristic                      | Treatment Sequence | Treatment Sequence | Overall |
|                                    | $T > R$ ($n = 9$)  | $R > T$ ($n = 9$)  |         |
| Sex, n                             | Female 4           | 5                   | 9       |
|                                    | Male 5             | 4                   | 9       |
| Race, n                            | Black or African American 1 | 0 | 1       |
|                                    | White 8            | 8                   | 16      |
|                                    | American Indian or Alaska Native 0 | 1 | 1       |
| Ethnicity, n                       | Hispanic 2         | 0                   | 2       |
|                                    | Not Hispanic 7     | 9                   | 16      |
| Age, mean (min, max), y            | 32.2 (24.0, 44.0)  | 27.8 (20.0, 38.0)  | 30.0 (20.0, 44.0) |
| Weight, mean (min, max), kg        | 78.2 (63.2, 89.0)  | 75.2 (55.0, 91.8)  | 76.7 (55.0, 91.8) |
| Height, mean (min, max), cm        | 173.4 (153.0, 188.0) | 167.7 (158.0, 183.0) | 170.6 (153.0, 188.0) |
| Body mass index, mean (min, max), kg/m² | 26.1 (20.9, 28.8) | 26.7 (22.0, 29.8) | 26.4 (20.9, 29.8) |

R, treatment with intravenous methylprednisolone 1 g once daily; T, treatment with adrenocorticotropic hormone analog 80 U once daily.

Figure 1A shows the mean (standard error of the mean) concentration–time profiles of methylprednisolone on days 1, 3, and 5. Concentrations were similar on days 1, 3, and 5. The half-life of methylprednisolone is 2.5 hours. Methylprednisolone levels were close to or below the limit of quantitation after a 28-day washout period in period 2, indicating no carryover effect in period 2.

Figure 1B shows the mean (standard error of the mean) concentration–time profiles of cortisol on days 1, 3, and 5. Levels of cortisol were lower than baseline on days 1 and 5. The half-life of cortisol is approximately 24 hours.20 Cortisol levels were close to or below the limit of quantitation after a 28-day washout period in period 2, indicating no carryover effect in period 2.

Figure 1. Serum methylprednisolone (MP) and cortisol exposure after administration of intravenous methylprednisolone (IVMP) or adrenocorticotropic hormone (ACTH) analog. (A) MP and cortisol serum concentration–time profiles following IVMP administration. (B) Cortisol serum concentration–time profile following ACTH analog administration. Note difference in time scale for cortisol. Data shown as mean ± standard error of the mean; $n = 17$ for IVMP and $n = 18$ for ACTH analog. All data for every day are represented in the plots. However, there is an overlap in the data for some days.
Table 2. Change From Baseline Total Cortisol-Equivalent Exposure After Multiple Dosing (Day 5) of ACTH Analog (80 U Once Daily) and IVMP (1 g Once Daily)

| Drug         | Total Steroid AUEC* | Total Cortisol-Equivalent Exposure |
|--------------|---------------------|-----------------------------------|
| ACTH analog  | 3641                | 0.03 (0.01)                       |
| IVMP         | 133310              | \(P < .001\)                      |

*Natural log (ln)-transformed data (geometric mean).
ACTH, adrenocorticotropic hormone; AUEC, area under the effect curve; IVMP, intravenous methylprednisolone.

were no effects of sex or BMI on cortisol-equivalent exposure AUEC.

Blood Pressure and Blood Glucose
Changes from baseline for SBP, DBP, and MAP were relatively small and comparable for both ACTH analog and IVMP groups (data not shown). Blood glucose values (predose) for subjects on ACTH analog on days 1 to 5 were lower compared with predose baseline glucose values for subjects on IVMP.

Effects on Immune Cells
White Blood Cells. There was an increase in overall white blood cell (WBC) count as determined by clinical laboratory assessment. However, the increase in WBC count following ACTH analog dosing was smaller than that observed following IVMP dosing \(P < .05\); Table 3. Further analysis of the automated differentials suggested that this difference was likely due to a less profound increase in circulating neutrophils. In addition, ACTH analog administration resulted in significantly less decrease in lymphocyte count than did IVMP administration \(P < .05\), with greater recovery by day 5.

Immune Cells From Flow Cytometry
Consistent with the data reported for automated WBC differential counts, flow cytometry data demonstrated that IVMP treatment resulted in a decrease in the number of circulating lymphocytes. ACTH analog administration also led to a decrease in the number of circulating lymphocytes; however, the decrease was significantly lower with ACTH analog \(P < .05\); Figure 3. When specific types of lymphocytes were examined (T and B cells), the absolute number of T cells (total T cells, Th cells [data not shown], and T cytotoxic cells [data not shown]) decreased from baseline following both treatments, but the decrease for all the T cells and T-cell subtypes after administration of IVMP was significantly greater \(P < .05\). Absolute total B-cell counts after multiple doses (day 5) of ACTH analog or IVMP increased from mean baseline AUEC and values, although the difference was not statistically significant. Both treatments resulted in an increase in the absolute number of granulocytes, including neutrophils, but the increases in neutrophils and granulocytes were significantly greater following IVMP administration \(P < .05\).

Tolerability
No deaths and serious AEs were reported during this study. All AEs reported were mild in severity. Subject incidence for AE reporting was similar following both treatments. The most common AEs were dysgeusia, reported only in IVMP-treated subjects (10 \(37\%\) overall), followed by mild rash in 6 subjects (2 ACTH analog, 4 IVMP \(22\%\) overall), and nausea in 5 subjects (1 ACTH analog, 4 IVMP \(19\%\) overall). There were no clinically significant safety findings in laboratory parameters, ECG, or vital sign measurements.

Discussion
This study was conducted to compare key PD parameters potentially relating to mechanism of action and tolerability of subcutaneous ACTH analog and IVMP in healthy subjects, using dosage regimens of both drugs that have been commonly employed for treatment of MS exacerbations. Consistent with the literature, administration of IVMP decreased serum cortisol concentration\(^{19-22}\).
whereas administration of ACTH analog increased it. These observations are consistent with the anticipated pharmacologic response of cortisol for the respective treatments, whereby ACTH would be expected to stimulate cortisol release from the adrenals, and methylprednisolone, a potent glucocorticoid, would induce a negative feedback effect on endogenous cortisol secretion. 16,20 Although methylprednisolone reduces endogenous cortisol, its administration results in significant cortisol-equivalent steroid exposure. Despite its effect on cortisol secretion, ACTH analog 80 U administered subcutaneously daily for 5 days resulted in a significantly lower overall serum cortisol-equivalent exposure than IVMP 1 g administered daily for 5 days (~3% of IVMP). As the PK and cortisol responses after methylprednisolone dosing have been reported to be linear, 20–22 and based on measured total steroid exposure, administration of 80 U of ACTH analog would equate to approximately 30 mg of IVMP. This difference in cortisol-equivalent exposure for ACTH analog and IVMP lends support to the hypothesis that the efficacy of ACTH analog in immunemediated disease may not be because of its effects on endogenous steroid production, as equivalent efficacy for ACTH analog and IVMP in disorders such as MS exacerbations generally requires methylprednisolone treatment at doses significantly higher than 30 mg daily. 23 Free endogenous cortisol levels are approximately 5% in blood, and free methylprednisolone levels after IVMP administration are approximately 23%. 19 Accounting for differences in free concentrations for cortisol and methylprednisolone would result in an even greater difference in total cortisol-equivalent activity between ACTH analog and IVMP.

In general, ACTH analog and IVMP exhibited varying effects on the PD parameters evaluated in this study of healthy subjects. With regard to blood pressure, no differences between ACTH analog and IVMP were observed, whether considering DBP, SBP, or MAP. There were, however, differences between ACTH analog and IVMP effects on circulating immune cell populations. The anti-inflammatory and immunosuppressive effects of corticosteroids are at least partly due to their effects on modulation of inflammatory mediators produced by WBCs. Because ACTH may affect populations of circulating immune cells through interactions with the melanocortin receptors expressed on leukocytes, as well as by indirect effects resulting from endogenous corticosteroid production, the effects of ACTH analog and IVMP on lymphocytes and granulocytes counts were compared.

Interestingly, 80 U of ACTH analog reduced absolute numbers of circulating lymphocytes and increased circulating neutrophil counts to a lesser degree than did 1 g of IVMP. In addition, depression of circulating lymphocyte counts was less sustained following ACTH analog compared with IVMP administration. As noted above, similar doses of these 2 agents to those used in the current study are commonly used to manage exacerbations of diseases such as MS. These data support the possibility that the efficacy of 80 U of ACTH analog in an autoimmune disorder such as MS exacerbation could be accompanied by less systemic immunosuppression than the comparably employed IVMP dose of 1 g. In this open-label study there was no significant difference in the tolerability of ACTH analog (80 U subcutaneously daily for 5 days) and IVMP (1 g daily for 5 days). As this was a healthy-subject, open-label study with no placebo control, the clinical relevance of these differences in tolerability is unknown and remains to be investigated for patient populations.

The differences in the PD outcomes evaluated in this crossover study of healthy subjects are intriguing and support the possibility that the mechanism of action of ACTH analog in inflammatory and autoimmune diseases may differ from that of exogenous corticosteroids. However, extrapolation and relevance of these findings to clinical outcomes in patient populations is unknown and remains to be investigated.

**Conclusions**

Cortisol-equivalent exposure following single and multiple doses of IVMP was significantly greater than that observed following single and multiple doses of ACTH.

| Variable | Treatment | P Value |
|----------|-----------|---------|
|          | IVMP      | ACTH Analog |
|          | Day 3 | Day 5 | Day 3 | Day 5 | Day 3 | Day 5 |
| Total WBC (thousands/mm³) | 13.44 (3.33) | 8.18 (2.94) | 5.88 (3.57) | 5.41 (2.81) | < .0001 | < .0074 |
| % Neutrophils | 29.44 (7.03) | 24.72 (8.34) | 15.52 (8.33) | 8.18 (6.76) | < .0001 | < .0001 |
| % Lymphocytes | −22.62 (5.64) | −19.13 (6.65) | −9.62 (7.40) | −2.77 (7.55) | < .0001 | < .0001 |

Data shown as mean (standard deviation); n = 17 for IVMP, n = 18 for ACTH analog.

ACTH, adrenocorticotropin hormone; IVMP, intravenous methylprednisolone; WBC, white blood cell.
analog, as demonstrated by serum cortisol-equivalent mean AUEC ratios (ACTH analog:IVMP). Based on the measured serum cortisol-equivalent exposure and assuming linearity, administration of 80 U of ACTH analog would equate to approximately 30 mg of IVMP. As stated previously, the doses of IVMP and ACTH analog assessed in this study are commonly used for the treatment of MS exacerbations. The lower total steroid-equivalent exposure for ACTH analog and the differences in peripheral leukocyte phenotype seen after these doses of ACTH analog and methylprednisolone support the hypothesis that the mechanism of action of ACTH analog in the treatment of inflammatory and autoimmune diseases may extend beyond its impact on endogenous steroid production and/or that efficacious doses of ACTH analog may have benefit in the treatment of MS relapses with potentially less impact on circulating immune cell profiles than pulse-dose exogenous corticosteroids. Subject incidence for AE reporting was similar following both ACTH analog and IVMP in this open-label crossover study in healthy subjects. The relevance of these findings to the mechanism of ACTH analog as a therapy for patients with autoimmune and inflammatory diseases warrants further investigation.

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Author Contributions

Authors contributed to study activities in the following manner. Substantial contributions to study conception and design: S.B., P.M.B., and D.Y. Substantial contributions to acquisition of data: S.B., R.L., V.H., R.C., D.D., and M.N. Substantial contributions to analysis and interpretation of data: R.L., R.C., S.B., D.D., P.M.B., and D.Y. Drafting the article or revising it
critically for important intellectual content: R.L., S.B., P.M.B., and D.Y. Final approval of the version of the article to be published: all authors.

Declaration of Conflicting Interests
S.B., R.C., V.H., M.N., D.D., and P.M.B. are employees of Mallinckrodt Pharmaceuticals and hold stock or stock options in Mallinckrodt Pharmaceuticals. R.L. was an employee of Mallinckrodt Pharmaceuticals. D.Y. was an employee of Mallinckrodt Pharmaceuticals. He also holds stock in Mallinckrodt Pharmaceuticals. R.L. was an employee of Mallinckrodt Pharmaceuticals and hold stock or stock options in Mallinckrodt Pharmaceuticals. S.B., R.C., V.H., M.N., D.D., and P.M.B. are employees of Mallinckrodt Pharmaceuticals. He also holds stock in Mallinckrodt Pharmaceuticals.

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