

Pilot Meta-Analysis of HPA Axis Suppression Studies on Topical Corticosteroids using ADaM Datasets derived from Legacy Data

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ABSTRACT

Topical corticosteroids are widely used in dermatologic therapy because of their anti-inflammatory and anti-pruritic effects. They are categorized into “potency” classes according to their effect on dermal erythema, which is based on vasoconstrictive activity. There is suggestion that such “potency” may be related to systemic effects such as the suppression of hypothalamic-pituitary-adrenal (HPA) axis.

Six HPA axis suppression studies have been included for a pilot safety meta-analysis for topical corticosteroid products. These studies involved the use of topical corticosteroids across a spectrum of “potencies” in patients with psoriasis or atopic dermatitis. ACTH stimulation and plasma cortisol measurements were conducted before and after a period of use of the topical corticosteroid. To perform the pilot safety meta-analysis, ADaM ADLB datasets, derived via SAS ® 9.3 for the conversion of legacy data of these studies, were combined, also using SAS programming. HPA axis suppression was defined either by plasma cortisol level after ACTH stimulation alone (one criterion) or by a combination of basal, post-stimulation, and rise in plasma cortisol levels (3 criteria). The 90% and 95% confidence intervals for the proportion of subjects showing HPA axis suppression were evaluated.

This pilot study illustrates the power of using standardized datasets across studies for the comparison of corticosteroid activity, and the results present a consistency of relationship between dermal vasomotor “potency” and systemic effect (HPA axis suppression).

INTRODUCTION

Topical corticosteroids are a mainstay of dermatologic therapy because of their anti-inflammatory and anti-pruritic effects. Using the McKenzie-Stoughton vasoconstriction assay¹, topical corticosteroids have been classified according to their effect on dermal erythema into different “potency” levels². To test the hypothesis that potency thus defined is linked to the clinical effects of topical corticosteroids, we attempt to compare clinical effects of the products across a spectrum of topical corticosteroid potencies.

We start with a pilot study to investigate hypothalamic-pituitary-adrenal (HPA) axis suppression by topical corticosteroid products of different potencies with meta-analysis because in contrast to data on adverse events or efficacy, HPA axis suppression measures a single target of corticosteroid activity, i.e., the impact on endocrinologic function. However, there have been differences in defining HPA axis suppression. We use ACTH (Cortrosyn®) stimulation methodology; HPA axis suppression is defined in the labeling of Cortrosyn®³ by any one of three criteria (basal, post-stimulation, and rise in plasma cortisol levels), while pharmaceutical companies have relied on the post-stimulation level alone to define suppression. In our analyses, we have included the use of both definitions.

In order to perform our meta-analysis, it was necessary to have standardized data across the HPA axis suppression studies conducted by different pharmaceutical companies over a substantial time period. We have converted legacy data from an archive of topical corticosteroid studies in the electronic document room of the U.S. Food and Drug Administration into CDISC-compliant datasets, and used HPA axis suppression study data in this pilot study.

THE CDISC-COMPLIANT DATASETS FOR HPA AXIS SUPPRESSION STUDIES

Legacy datasets from topical corticosteroid studies have been converted into CDISC (Clinical Data Interchange Standards Consortium) SDTM (Standard Data Tabulation Model) datasets and ADaM (Analysis Data Model) datasets by using SAS 9.3, according to an updated CDISC SDTM Implementation Guide (v 3.2) and ADaM Implementation Guide (v1.0)^{4,5}. The standard datasets for the HPA axis

suppression studies in this pilot analysis has been validated through Pinnacle 21 software. We have worked on 11 New Drug Application (NDA) submissions with over 60 clinical trials and more than 740 SDTM datasets, including efficacy/safety studies, dermal safety studies and HPA axis suppression studies. Potency information on the products is shown in Table 1.

Drug	Cortico-steroid 1	Cortico-steroid 2	Cortico-steroid 3	Cortico-steroid 4	Cortico-steroid 5	Cortico-steroid 6	Cortico-steroid 7	Cortico-steroid 8	Cortico-steroid 9	Cortico-steroid 10	Cortico-steroid 11
Potency Class	Class 1 Super-high	Class 1 Super-high	Class 5 Lower mid-strength	Class 5 Lower mid-strength	Class 3 Upper mid-strength	Class 1 Super-high	Class 1 Super-high	Class 6 Mild	Class 1 Super-high	Class 1 Super-high	Class 3-4 Mid-strength

Table 1. Topical Corticosteroid Products with Legacy Data Standardized into CDISC-compliant Datasets

The pilot meta-analysis on HPA axis suppression used ADaM datasets from 6 NDA studies. The potencies for the topical corticosteroid products in the studies for pilot meta-analysis are provided in Figure 1, which shows 3 studies with topical corticosteroids of potency from super-potent to mid-strength (Class 1 to 4) in psoriasis patients, and 3 studies with topical corticosteroids of potency from lower mid-strength to mild (Class 5 to 6) in atopic dermatitis patients. All studies involved testing for HPA axis suppression with ACTH (Cortrosyn®) stimulation.

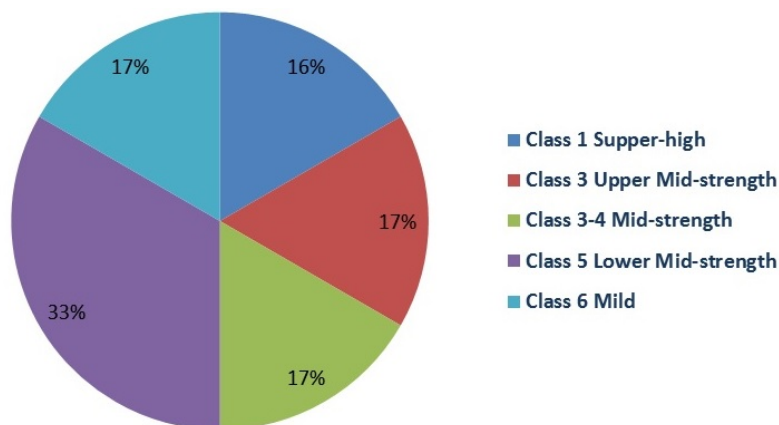


Figure 1. Potencies for the Topical Corticosteroids among the Six Studies on HPA Axis Suppression for Pilot Meta-analysis

PILOT META-ANALYSIS ON HPA AXIS SUPPRESSION STUDIES

To perform pilot safety meta-analysis for the HPA axis suppression studies, ADaM ADLB datasets from the selected 6 NDA studies were combined in SAS 9.3. The ADLB datasets for the three studies on atopic dermatitis were pooled across potencies, and the ADLB datasets for the three psoriasis studies were similarly pooled.

Normal HPA axis function after ACTH stimulation is defined in the labeling of Cortrosyn® as follows: 1) pre-stimulation plasma cortisol (basal) level should exceed 5 micrograms/dL; 2) the 30-minute post-stimulation cortisol level should show an increment of at least 7 micrograms/dL above the basal level; and 3) the 30-minute post-stimulation cortisol level should exceed 18 micrograms/dL³. However, most pharmaceutical companies only use one criterion to define HPA axis suppression, viz., the 30-minute post-stimulation cortisol level not exceeding 18 micrograms/dL.

In the meta-analysis ADLB datasets, for each combined potency group, the datasets were adjudicated with the same definition for HPA axis suppression by one or three criteria, at the baseline and at the end of treatment visit for each study subject: this allowed for the exclusion of those subjects who already showed HPA axis suppression before treatment by one or three criteria, respectively, and enabled the suppression rates at the end of treatment visit to reflect the effects from the study treatment.

Using SAS 9.4, we assigned two variables (CRIT1 and CRIT2) for the two evaluation methods for the detection of HPA axis suppression: CRIT1 represented suppression using 3 criteria and CRIT2 using 1 criterion. With the determination of HPA axis suppression based on CRIT1 or CRIT2 in each study subject, the suppression rates were calculated for each topical corticosteroid product or for each combined potency group. The codes to generate the suppression variables, CRIT1 and CRIT2, are listed below (partially).

```
DATA ADLB_SUP;
SET AD_1;
CHANGE=AVAL2-AVAL1;
IF AVAL1 > 5 AND CHANGE > = 7 AND AVAL2 > 18 THEN CRIT1='N';
ELSE CRIT1='Y';
LABEL CRIT1='Adrenal Suppression at 3 Criteria';
IF AVAL2 > 18 THEN CRIT2='N';
ELSE CRIT2='Y';
LABEL CRIT2='Adrenal Suppression at 1 Criterion';
LABEL AVAL1='Pre-dose Cortisol Level';
LABEL AVAL2='Post-dose Cortisol Level';
LABEL CHANGE='Difference between Pre-dose and Post-dose Cortisol Level';
RUN;
```

The HPA axis suppression rates with 95% and 90% confidence intervals (CIs) in the combined ADLB datasets were calculated using Fisher's Exact test and compared between diseases and drug products under the different evaluation criteria described above through SAS 9.4. Confidence intervals for binomial proportions were readily generated via PROC FREQ. The codes to generate the 95% (i.e. $\alpha=0.05$) and 90% (i.e. $\alpha=0.10$) CIs for the suppression rates at 3 criteria (CRIT1) are listed below, and those for generation of rates at one criterion (CRIT2) are similar.

```
proc freq data=FPL_ET3 ORDER=formatted;
EXACT BINOMIAL;
tables CRIT1/ BINOMIAL (exact) alpha=0.05;**CI=95%**;
format CRIT1 $CRIT.;
run;
proc freq data=FPL_ET3 ORDER=formatted;
EXACT BINOMIAL;
tables CRIT1/ BINOMIAL (exact) alpha=0.10;**CI=90%**;
format CRIT1 $CRIT.;
run;
```

ANALYSIS FINDING

HPA axis suppression rates of the combined studies were obtained for the topical corticosteroids of higher potency and lower potency groups through SAS programming. The results of combining studies for HPA axis suppression rates with topical corticosteroids of higher potency (Class 1 to 4) as well as corresponding rates with topical corticosteroids of lower potency (Class 5 to 6) are shown in Table 2.

Topical Corticosteroid Potency Class	Proportion with Suppression using 3 Criteria*			Proportion with Suppression using 1 criterion**		
	Suppression Rate (%)	95% CI	90% CI	Suppression Rate (%)	95% CI	90% CI
[Class1~4]	36.0	27.1-45.7	28.4-44.2	13.5	8.1-20.7	8.8-19.6
[Class5~6]	10.8	5.9-17.8	6.5-16.7	0.8	0.0-4.4	0.0-3.7

*The 3 criteria are: 1) Pre-stimulation plasma cortisol level did not exceed 5 micrograms/dL; 2) the 30-minute level did not show an increment of at least 7 micrograms/dL above the basal level; 3) The 30-minute post-stimulation level did not exceed 18 micrograms/dL.

**The criterion is: the 30 minute post- stimulation cortisol level did not exceed 18 micrograms/dL.

Table 2. Suppression Rates by Meta-Analysis of HPA Axis Suppression Studies for Topical Corticosteroids

The confidence interval for the proportion of subjects showing suppression by topical corticosteroid products in the higher potency groups for psoriasis does not overlap with that by topical corticosteroids in the lower potency groups (either 95% or 90% confidence interval).

OTHER CONSIDERATIONS

For this meta-analysis, CDISC-standardized datasets (ADaM ADLB) of similar HPA axis suppression studies were combined, and standard variables for suppression detection were used through SAS programming. It illustrates that SAS is a powerful and efficient tool for standard data preparation and statistical analysis.

HPA axis suppression studies for topical corticosteroid products are usually based on sample sizes of about 50 subjects at the outset of the study. With meta-analysis, similar trials can be combined to give a more precise estimate of average treatment effect, and increase the ability to make data-based assessments. Rather than emphasis on P-values, confidence intervals in our pilot meta-analysis provide a readily understandable estimate.

Although a relationship between the effect of topical corticosteroids on dermal vasoconstriction and clinical safety and efficacy has been the basis of choice in dermatologic therapy with these drug products, a formal demonstration of this relationship has not been documented. Clinical trials usually study one or two topical corticosteroids, and the collection of data in non-standard format does not lend them to comparative analysis expediently. Moreover, topical corticosteroids are used for a myriad of conditions for their anti-inflammatory and anti-pruritic effects, and the interpretation of clinical effectiveness is complicated by multiple factors such as the condition being treated, disease severity, body surface area involvement, concomitant medications, etc.

In this meta-analysis pilot project, we have examined the safety of topical corticosteroids using the HPA axis suppression system. The use of ACTH stimulation to test for secondary adrenal suppression is well established. With legacy data converted into CDISC-standard format, we are able to conduct meta-analysis of HPA axis suppression rates using studies designed for maximal product use. However, we acknowledge that the populations in these studies may be a confounding factor, as atopic dermatitis studies involved the use of lower potency products, while the higher potency products are generally used for psoriasis due to the fact that this condition is less responsive to treatment.

Our finding of non-overlapping confidence intervals (90% and 95%) for HPA axis suppression rates by lower potency versus higher potency topical corticosteroids regardless of applying one or three criteria for suppression (Table 2) shows that at least for this systemic safety parameter, there is a significant difference in effect between such potencies. It establishes a relationship between potency and systemic safety.

Since this is a pilot study with a relatively small sample of studies, a meta-analysis with standardized data from more HPA axis suppression studies would help to confirm this relationship. The automation of analysis via SAS programming is also expected to facilitate our next study phase.

CONCLUSION

This pilot study illustrates the power of using standardized datasets across studies for the evaluation of corticosteroid effects. It also illustrates that the analysis for dermatological clinical trials is easily performed with SAS programming. The results demonstrate the relationship between dermal vasomotor “potency” and systemic effect (HPA axis suppression).

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