Pilot Meta-Analysis for HPA Axis Suppression Studies through ADaM Datasets from derived Legacy Data

Lillian (Aijun) Qiu and Hon-Sum Ko

DDDP, ODE3, CDER, FDA, Silver Spring, MD 20993

Introduction

- Topical corticosteroids are a mainstay of dermatologic therapy because of their anti-inflammatory and anti-pruritic effects and have been classified according to their effect on dermal erythema into different potency levels based on vasoconstriction activity.
- It has been postulated that such potency levels may relate to drug safety and efficacy, but formal proof is wanting.
- We intend to examine potency levels of topical corticosteroids in relation to systemic safety using hypothalamic-pituitary-adrenal (HPA) axis suppression with Cortrosyn® stimulation, which represents a relatively clean system with few confounders.
- HPA axis suppression is the labeling of Cortrosyn® can be established by any one of three criteria (basal, post-stimulation, and rise in plasma cortisol levels); however, many studies base suppression on the post-stimulation level alone.
- In the pilot study described below, the data from HPA axis suppression studies conducted by different pharmaceutical companies over a substantial time period have been standardized into CDISC-compliant datasets.

Materials

- Legacy data from 11 New Drug Application (NDA) submissions containing a total of 60 trials have been converted into 740 SUTM datasets, including efficacy/safety studies, HPA axis suppression studies, and dermal safety studies. Potency information on the products is shown in Table 1.

Methods (Continued)

- The pilot meta-analysis on HPA axis suppression studies used Analysis Data Model (ADaM) from 6 NDA studies. The potencies for the topical corticosteroid products in the studies for pilot meta-analysis are involved the use of lower potency products, while the higher potency products would generally be used for psoriasis due to the fact that this condition is less responsive to treatment. A meta-analysis with standardized data from more HPA axis suppression studies would help to combine the findings of HPA axis suppression rates using studies designed for maximal product use.
- With legacy data converted into CDISC-standard format, we are able to conduct meta-analysis of HPA axis suppression rates at 3 criteria (CRIT1) are listed below, and those for generation of rates using studies designed for maximal product use. 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 suppression criteria through SAS v9.4.

Results

Table 2 shows 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).

Discussion

- 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 an overall estimate of average treatment effect to make up for the findings of inadequate sample size, and hence increasing the power.
- 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.
- The interpretation of clinical effectiveness of topical corticosteroids is complicated by multiple factors, e.g., the condition being treated, disease severity, body surface area involvement, concomitant medications, etc., while HPA axis studies afford a cleaner system for drug effect. The formulation poses substantial effects via its vasomotor potency which influences absorption and local toxicity.
- The populations in these studies might be a confounding factor, as atopic dermatitis studies often involved concomitant medications, etc., while HPA axis studies afford a cleaner system for drug effect. The formulation poses substantial effects via its vasomotor potency which influences absorption and local toxicity.

Conclusions

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