Chapter 17
Pharmacometrics in Dermatology

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17.1 Introduction

There is a paucity of published literature on the application of pharmacometrics methods in dermatologic drug development. This can be attributed to unique challenges associated with development of new agents in this disease area as described in a review by Eaglstein et al. (2009). The market for drugs for dermatologic conditions is relatively small as compared to that for other therapeutic areas such as heart disease, neurological conditions, or cancer thus reducing the economic incentive to develop these drugs. The endpoints for assessing efficacy have a considerable subjective element involved in their quantitation. Topical agents still play a significant role in the treatment of skin diseases; newer systemic medications are usually developed after the drug has been approved for another indication that shares the underlying pathophysiology with the skin condition. This has been the case in the inflammation disease area where some of the drugs approved for the treatment of rheumatoid arthritis have been successfully developed further for the treatment of plaque psoriasis.

It can therefore be surmised that potential for pharmacometric applications in dermatology remains largely unappreciated. The commonly held belief is that there are limited opportunities to utilize model-based methods in development of dermatologic agents. Nevertheless, there are a few noteworthy examples which clearly showcase the value these methodologies bring towards optimizing the clinical development strategy and facilitating decision making. The ensuing sections will acquaint the reader with examples where quantitative methods have been successfully employed to streamline dermatologic drug development.

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17.2 Pharmacometrics in Early Drug Development

In early stages of development, availability of richer pharmacokinetic (PK) data, biomarkers, and short-term efficacy data, allow the use of mechanistic pharmacokinetic–pharmacodynamic (PK–PD) models to characterize relationships between exposure and response variables. Such quantitative approaches can be effectively employed to establish a minimum effective dose, identify an optimal dose range, and inform futures study design. The ultimate goal at this milestone is to gain a sufficient understanding of the safety and efficacy characteristics of the drug candidate to increase the likelihood of success and minimize the chance of adverse events in the next stage in development.

17.2.1 PK–PD Targets for Antibacterial Drug Development

Infectious disease is not a disease area that one typically associates with dermatology. However, infections of skin, such as complicated skin and skin structure infections (cSSSIs) and impetigo, are very common. These infections caused by gram-positive or gram-negative pathogens can be minor in nature which can be treated with topical antibacterial products, or can be serious requiring systemic antibacterials and hospitalization. The general paradigm followed for antibacterials during early clinical development involves evaluating the PK–PD of candidates in preclinical infection models (animal (Ambrose et al. 2007) or hollow-fiber models (MacGowan et al. 2001)) where PK–PD targets or clinically meaningful thresholds are identified. The main objective of these experiments is to identify the optimal antimicrobial plasma concentration–effect curve that will provide the desired efficacy. The PD parameters usually investigated in these preclinical models are the area under the curve (AUC)/minimum inhibitory concentration (MIC), maximum plasma concentration (C_{max})/MIC and $T>$MIC (i.e., time that the serum concentrations remain above MIC; Ambrose et al. 2007). These evaluations are typically based on free drug exposures and not total exposures. Use of total exposures is usually employed for drugs which do not exhibit cross-species differences in protein binding.

Dose fractionation studies in the preclinical infection models allow for identification of the PD parameter that is best associated with the antimicrobial effect (Ambrose et al. 2007). For β-lactams (penicillins, cephalosporins, carbapenems, monobactams), $fT>$MIC has been identified as the PD parameter. For drugs like vancomycin, azithromycin, clarithromycin, linezolid, doxycycline, and tigecycline $f\text{AUC}_{0\text{-}24}$: MIC is the PD parameter. Daptomycin has both $f\text{AUC}_{0\text{-}24}$: MIC and C_{max}: MIC as PD parameter. Daptomycin is given once daily (QD) and thus $\text{AUC}_{0\text{–}24}$ and C_{max} are highly correlated, which may explain lack of differentiation between the two PD parameters.

This PD parameter is then used to define the PD threshold based on criteria such as achieving bacteriostasis or achieving at least 1-log kill. Selection of these criteria is beyond the scope of this discussion and the reader is referred to the literature for further details (MacGowan et al. 2001). Defining the PD parameters may not

Table 17.1 PD targets for evernimicin. (Adapted from Drusano et al. 2001)

Organism	AUC/MIC ratio		
	Stasis target	Log drop target[a]	90% E_{max} target
Streptococcus pneumoniae	115.7	239.4	1716.4
Staphylococcus aureus	163.4	330.1	830.8
Enterococcus faecalis	59.6	85.4	764.4

Protein binding was identical between the animal species and humans. Hence, no correction was made to the PD targets

[a] Log drop targets were 3-$\log_{10}$ unit decline for *S. pneumoniae*, 2-$\log_{10}$ unit decline for *S. aureus* and 1-$\log_{10}$ unit decline for *E. faecalis*

always be simple, especially when more than one PD parameter is associated with antimicrobial effect; more mechanistic PK–PD models may be needed to characterize the PK–PD relationships in such cases.

The PD threshold thus identified provides the dosing rationale for the design of the clinical studies. Dose selection can be based on the ability of the doses to meet the PD threshold in a target number (percent) of patients. The latter can provide the basis of conducting a dose-ranging evaluation; for instance, clinical trial simulations (CTS) based on the PK–PD model can predict the dose range that would meet the PD criteria in 80–100% of the patients to maintain maximal efficacy. Such a simulation approach has been successfully applied to several antibacterial agents for selection of doses in phase 2.

An example illustrating the application of the above approach for evernimicin was reported by Drusano et al. (2001). MIC distribution of clinical isolates, PD targets identified in animal models of infection and protein-binding characteristics of the drug were used in conjunction with the population PK model for rational dose selection for phase-2/3 trials. The PD targets (Table 17.1) were identified for three different organisms in a neutropenic mice thigh infection model.

The population PK model developed using the data from phase-1 studies in healthy volunteers was used to perform Monte Carlo simulations to obtain exposures (AUC) in subjects at each dose. The simulated exposures were then used to calculate the fraction of subjects who met the PD targets listed in Table 17.2 at each MIC; the overall response for the pathogens was calculated at a given dose using the frequency of a given MIC in the MIC distribution.

Based on the above results it is clear that a dose of 6 mg/kg would achieve stasis for all organisms given the MIC distribution typically observed. However, for enterococci, a 9 mg/kg dose would be advantageous when maximal effect is desirable.

The above strategy can be used to select doses for new candidate molecules for conducting phase–2 trials using preclinical and healthy subjects' data.

17.2.2 Target Site PK–PD

An important consideration for drugs for dermatological indications is to understand the link between local drug exposure and clinical outcome. For example, in

Table 17.2 Target achievement for evernimicin. (Adapted from Drusano et al. 2001)

Dose (mg/kg/day)	% Attainment of response (±SD)								
	Streptococcus pneumoniae			*Staphylococcus aureus*			*Enterococcus faecalis*		
	Stasis	Log drop (3 $\log_{10}$ units)	90% E_{max}	Stasis	Log drop (2 $\log_{10}$ units)	90% E_{max}	Stasis	Log drop (1 $\log_{10}$ units)	90% E_{max}
6	100	99.9	95.87	91.64	71.79	34.25	99.7	99.41	58.14
	±0.0	±0.009	±0.07	±0.2	±1.89	±0.68	±0.11	±0.11	±2.82
9	100	100	97.71	96.83	85.10	50.74	99.93	99.93	74.84
	±0.0	±0.0	±0.02	±0.08	±0.84	±0.84	±0.004	±0.004	±0.59

the case of antibacterials that treat skin infections, ability to achieve target concentrations in the skin is the key to efficacy. The PD parameters established for a candidate molecule as discussed above usually relate plasma/serum concentrations to antibacterial activity. For this correlation to be valid, it is important to establish that the ratio of drug exposure in the skin to that in serum/plasma approaches 1. The above-mentioned consideration regarding correlation between dermal availability and clinical outcome is particularly important for topically applied agents. McClain et al. (2009) evaluated cutaneous exposures of topical corticosteroids relative to that achieved by oral prednisone and concluded that their skin concentration correlated well with their efficacy.

Both local drug concentrations and the impact on disease-related biomarkers can provide valuable understanding regarding the mechanism of action as well as the exposure–response (ER) relationship in the skin. The success of this endeavor depends on quantifying concentrations in the relevant skin compartment. This is a challenging task owing to factors such as availability of a sensitive analytical method, sampling considerations and invasiveness of sampling methods, physiochemical properties of the drug, and robustness of the PD markers/biomarkers.

Dermal microdialysis is a useful minimally invasive sampling technique, which can be used to determine drug levels in the extravascular fluid in the skin. Microdialysis involves the use of a probe (a small semipermeable hollow fiber membrane) that can be inserted into tissue and perfused with a physiological solution at a constant rate. Free, unbound solutes can freely cross the membrane by passive diffusion due to a concentration gradient and can be used to sample the extravascular space continuously. The biggest advantage of this technique is the ability to measure unbound drug concentrations in the target tissue thus providing a direct correlation between the exposure driver at the site of action and the associated response. An exception to the above would be drugs which act intracellularly. The technique can be applied to both exogenous and endogenous agents in the extracellular space. For instance, microdialysis has been used to measure the baseline levels of cytokines in psoriatic plaques (IL-2, IL-6, IL-18, IL 23) and changes induced by treatment with fumaric acid derivatives (Salgo et al. 2011). However, the approach has operational limitations and may not work well for lipophilic, protein-bound, and high molecular weight drugs due to poor recoveries. A very sensitive assay capable of detecting low free drug concentrations may overcome this limitation. More recently, novel membrane-free probes and wearable multichannel pumps have overcome these limitations and have been used for prolonged sampling of lipophilic molecules in psoriatic lesional skin (Bodenlenz et al. 2012).

17.3 Population Pharmacokinetics (PK)

Collection of sparse PK samples in patients in outpatient clinical studies enables characterization of PK properties in the target population. PK analysis using a population-based approach provides an understanding of patient-specific charac-

teristic that may impact exposure and helps in deriving dosing recommendations in conjunction with exposure response (ER) analyses. Development of a population PK model also allows for simulation of different dosing regimens that can be subsequently tested in a clinical study. The typical approach for conducting population PK analyses is as follows:

- Develop a structural model that allows elucidation of concentration-time profile of the drug in the patient population.
- Incorporate random effects on structural model parameters that describe between patient/subject variability (also termed as interindividual variability), interoccasion variability, and residual variability.
- Develop a covariate model from the list of plausible patient-specific characteristics that may help explain some of the random variability in structural model parameters.

Population PK analyses for dermatologic compounds have primarily been reported in the psoriasis disease area. Plaque psoriasis is a chronic inflammatory skin disease driven by dysregulation in the immune system (Nestle et al. 2009). Cellular proliferation due to interplay of cytokines ultimately results in skin lesion formation, characterized by red, scaly, raised plaques. While no cure for psoriasis exists, symptomatic management can be achieved by therapies such as topical agents, phototherapy, systemic immunosuppressants as well as biologics. Among these, biologics have emerged as the most promising treatment options in reducing the burden of disease. These agents target cytokines such as IL-12 and IL-23 (ustekinumab), or tumor necrosis factor (TNF; etanercept, adalimumab, and infliximab). Another previously approved biologic that targets T-cells (efalizumab) has been withdrawn from the market.

The PK characteristics of biologics differ from conventional small molecules due to their unique disposition characteristics; receptor mediated clearance may lead to nonlinear PK depending on the concentration range studied. Adalimumab and infliximab are known to exhibit nonlinear PK characteristics (Nestorov 2005). However, discerning such PK attributes is usually difficult from outpatient data where factors such as the dose range studied, time points for PK sampling, and sparseness of collected data may limit the exploration of complex mechanism-based models. In such instances, a simple model may be deemed sufficient and practical to pursue future work. This is clearly evident from the example by (Nestorov et al. 2004) where a stepwise time function was modeled for apparent clearance (CL/F) and apparent volume (V/F) after attempts to fit a continuous sigmoidal function were unsuccessful for etanercept. The CL/F was found to be approximately 80 % of the steady state value before week 8 of dosing, thereafter it peaked to approximately 120 % between weeks 4 and 8 and then gradually tapered down to achieve steady state values after week 8. These time effects on clearance were postulated to be arising from the redistribution of etanercept and TNF-binding sites between the blood and the poorly perfused skin compartment (site of action).

Across the various biologic therapies, effect of body size measures such as body weight or body mass index (BMI), as clinically important determinants of drug

clearance has consistently been reported. For instance, ustekinumab exhibits a 57 % and 37 % higher CL/F and V/F, respectively, in patients weighing greater than 100 kg compared to those who weigh less than 100 kg (Zhu et al. 2009). Similarly for efalizumab, patients weighing 137 and 57 kg had a 37 % higher and 30 % lower CL/F, respectively, compared to the typical population value of 1.29 L/day (Sun et al. 2005). Such assessments are particularly relevant in psoriasis patients since they tend to have higher body weights compared to the general population. Consequently, these results can lead to clinically important implications with respect to dosing adjustments based on body size considerations. The weight-based dosing recommendations for ustekinumab were supported by the magnitude of PK change in the proposed dosing cohorts (Lebwohl et al. 2010). This example is described in detail in the next section.

Once the population PK model is finalized, it can be further used to simulate PK data under alternate dosing regimens. Such an evaluation can enable extrapolation across different dosing scenarios and provide the rationale for supporting dose modification or even a new regimen. This can be evidenced from an example by Nestorov et al. (2004), who conducted a modeling and simulation exercise to support a novel dosing regimen for etanercept. Data from three clinical studies with doses of 25 mg QW (once weekly), 25 mg BIW (twice a week), and 50 mg BIW, were used to develop a population PK model. The model included covariate effects on CL/F (gender, weight, and time) and V/F (weight). This model was used to simulate concentration–time profiles for after a new regimen involving the administration of 50 mg once a week (50 QW). The simulated steady state concentrations for this regimen demonstrated concordance with the observed profiles for 25 mg BIW. Additionally, the simulations were in good agreement with additional PK data from 84 patients receiving 50 mg QW, which provided external validation for the model. Based on these results, it was concluded that the concentration–time profile arising from 50 mg QW could be predicted with high precision; the overlap with 25 mg BIW suggested high probability of achieving consistent efficacy and safety between the two regimens.

17.4 Exposure Response (ER) Relationships

An understanding of the relationship between drug exposure (dose or summary PK measures, such as C_{max}, C_{min}, C_{avg}) and response (efficacy and safety) is critical to establishing the benefit–risk profile of a drug candidate. The food and drug administration (FDA) guidance on ER relationships (FDA 2003) highlights the utility of characterizing these relationships in drug development and also illustrates how this knowledge can facilitate regulatory decision making. ER relationships can provide support for primary evidence of efficacy or safety; they can also support benefit–risk evaluation in subpopulations or dosing adjustments (including regimens, formulations, route of administration). Characterizing ER has proven valuable in the development of new therapies in the psoriasis disease area.

17.4.1 Using ER to Understand the Impact of Patient Specific Factors on Efficacy of Psoriasis Drugs

ER assessment for psoriasis drugs has typically aimed at establishing a relationship between the measure of disease severity termed as psoriasis area and severity index (PASI) and drug exposure in patients with moderate to severe plaque psoriasis. PASI scores reflect a weighted average calculated from severity and area of psoriatic plaques. In clinical studies for psoriasis, the primary endpoint is the proportion of patients achieving $\geq 75\%$ improvement in PASI score from baseline, which is referred to as PASI 75 response. The section below presents examples where ER relationships for PASI endpoints for two approved biologics and one small molecule in development provided valuable insights into the interpretation of the efficacy profile along with elaboration of key determinants of efficacy.

Hutmacher et al. (2007) developed a population ER model for PASI 75 for etanercept with pooled data from three randomized, placebo-controlled clinical trials using a sequential PK–PD analysis approach. Predicted cumulative AUC (PCAUC) derived using the post hoc parameters from the final PK model was deemed as the most suitable exposure measure (compared to cumulative dose or predicted through concentrations) to evaluate the ER relationship. The mixed effects logistic regression model for PASI 75 is given by the following equation:

$$\text{Logit}\left[\text{P}(\text{event}=1)\right] = \textit{Intercept} + \textit{placebo time effect} + \textit{drug effect},$$

where intercept reflects the baseline probability; placebo time effect is given by the product (slope*time) and drug effect is given by the following model:

$$\text{drug effect} = E_{\max} * \frac{(\text{PCAUC}^{*})^{\gamma}}{\text{EC50}^{\gamma} + \text{PCAUC}^{*\gamma}}.$$

In the above equation, $E_{\max}$ is the maximum drug effect, EC50 is the exposure that achieves 50% of the maximum drug effect, γ is the hill coefficient, and PCAUC* is an apparent exposure expressed as PCAUC (1-exp(-keot)) to capture the delay between drug exposure and effect (characterized by rate constant keo). It should be noted that the placebo model has limited interpretation due to its simple structure, i.e., linearity with time.

Interpatient variability was allowed to change with time in the model. The final model included race and sex effects on the intercept, baseline PASI and prior systemic/phototherapy on $E_{\max}$, an age effect on keo and a weight effect on EC50. The analysis predicted a 130% increase in EC50 for a twofold weight change. Despite the variable selection algorithms selecting the weight effect on EC50, inspection of the results indicated that the model could not ascertain effectively whether difference in potency (EC50) or temporal delay (keo) was accounting for the observed weight-based trend in the data. Ultimately, it was concluded using other analyses that dose adjustment was not warranted for any subgroup of patients.

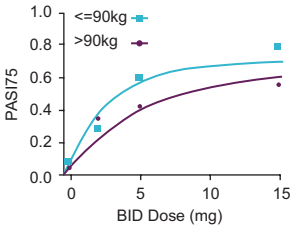

Fig. 17.1 Observed and model-predicted PASI 75 by median weight at week 12 for tofacitinib. Observed data are represented by *symbols* and model predictions by *solid lines*; data from a phase 2b dose-ranging study of tofacitinib in patients with moderate to severe chronic plaque psoriasis. (Adapted from Gupta et al. 2011)

A similar weight-based phenomenon was observed for tofacitinib an investigational psoriasis drug, in a 12-week phase 2b dose-ranging study (placebo, 2, 5, and15 mg BID) in patients with moderate to severe chronic plaque psoriasis. Longitudinal ER modeling of PASI scores revealed body weight as being a significant covariate of drug effect. Weight was found to impact pharmacodynamic potency as well as the time delay rate constant in a modified indirect response model (Gupta et al. 2011). As was found with etanercept, the model could not explain whether dose adjustment or longer trial duration was required for the heavier subgroup to achieve the same level of response as their lighter counterparts. Figure 17.1 shows the predicted PASI 75 response rate for two weight cohorts stratified by median weight (90 kg) at week 12 (time for primary endpoint evaluation).

Given the small sample size and the uncertainty associated with the ER relationship, it was proposed to continue to explore 5 and 10 mg BID as a fixed dosing regimen for a longer duration (up to 52 weeks) in the phase 3 studies in psoriasis patients. It was anticipated that the large sample size in the phase 3 program would provide an adequate number of patients to detect any significant differences in efficacy over time with respect to weight.

Another example of a population-based exposure–PASI relationship was reported for the IgG1-based monoclonal antibody-ustekinumab (Zhou et al. 2010). Data from two phase-3 studies ($n=1312$) for psoriasis patients receiving 45 or 90 mg were used to develop an indirect response model. The model assumed the formation and remission rates of the psoriatic plaques to be zero order (kin) and first order (rate constant: kout), respectively. The drug effect inhibited the formation rate as shown below:

$$\frac{\mathrm{d}(\mathrm{PASI})}{\mathrm{dt}} = kin * (1 - drug\ effect - placebo\ effect) - kout * PASI$$

$$\text{drug effect} = E_{max} * \frac{\mathrm{Cp}}{\mathrm{IC50} + \mathrm{CP}}$$

$$\text{placebo effect} = plbmax * (1 - \exp(-keo * time))$$

$$kin = kout * baseline\ PASI.$$

E_{max}, IC50, and γ have their usual interpretations as described above; *C*p represents ustekinumab serum concentrations that were derived from the final PK model (one compartment model with first order absorption and elimination). Placebo effect also inhibited the formation rate. In the above equation, plbmax describes the steady state inhibition and keo is the rate constant governing the time course of placebo effect. Interpatient variability on PD parameters (kin, kout, and IC50) was assumed to follow a log normal distribution and a combination of proportional and additive errors was used to model the residual variability. The model provided adequate fits to the observed data and was deemed acceptable by the goodness of fit plots and simulation-based diagnostics. An exhaustive pool of covariates was evaluated following the base-full-final model approach. However, since the covariates in the full model could not account for interpatient variability in the PD parameters (283, 60, and 54%, for IC50, kin, and kout, respectively), they were not retained in the final model.

The authors noted that there was a significant overlap of exposures between patients less than 100 kg receiving 45 mg and those heavier than 100 kg receiving 90 mg. This observation had previously been applied to justify the two-tiered fixed dosing regimen for ustekinumab in psoriasis patients (Lebwohl et al. 2010). The authors in this manuscript reasoned that the 100-kg weight cut point was optimal since the changes in efficacy paralleled the changes in systemic exposure, i.e., the PASI 75 response rates among heavier patients receiving 90 mg (74%) and lighter patients receiving 45 mg (77%) were comparable. The proposed regimen was:

- For patients ≤100 kg, 45 mg initial dose (and 4 weeks later) and every 12 weeks thereafter
- For patients >100 kg, 90 mg initial dose (and 4 weeks later)and every 12 weeks thereafter

However, the US FDA disagreed with this assessment and opined to the Dermatologic and Ophthalmic Drugs Advisory Committee that the dosing regimen for ustekinumab was suboptimal in terms of benefit that it yielded to heavier weight patients (FDA 2008). The FDA based their recommendation on an exposure (AUC)–PASI relationship (Fig. 17.2) developed from the two studies mentioned above which revealed that instead of a two-tiered dosing approach the patients would stand to benefit more from an alternate three-tiered regimen (<60, ≥60–<90, and ≥90 kg) that could yield PASI response rates similar to those arising from the administration of 90 mg to all subjects. Table 17.3 shows the predicted response under the different dosing scenarios based on the exposure–PASI relationship. Table 17.3 illustrates the projected improvement in clinical outcome in heavier patients receiving the alternate regimen as proposed by the FDA.

This example clearly demonstrates the successful utilization of an ER relationship to assess the impact of a key patient-specific factor (body weight) on clinical response. The example further shows how the insights gained from the ER relationship can be used to recommend dosing modifications in patient subgroups that stand to benefit from an alternate regimen.

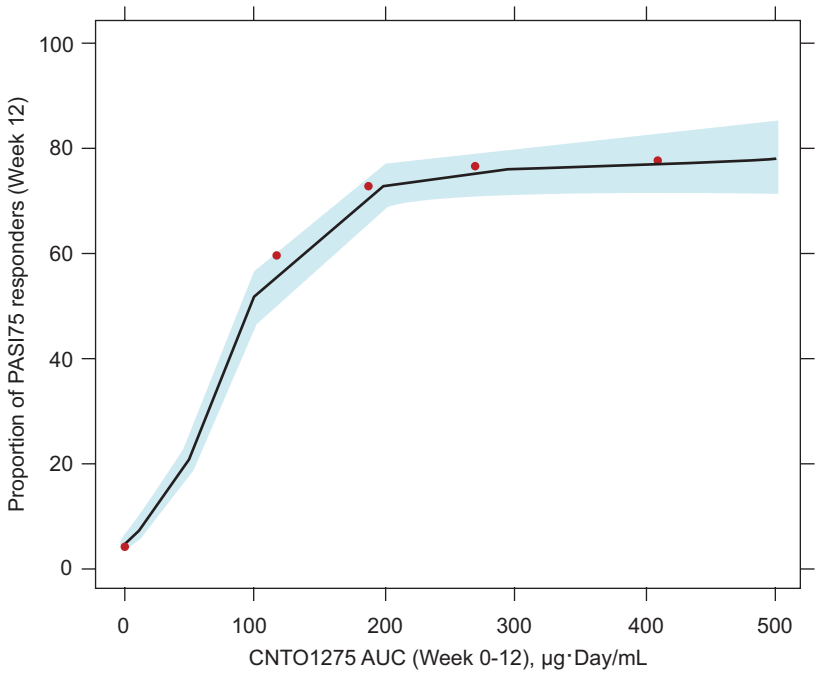

Fig. 17.2 Exposure (AUC)–response (PASI 75) relationship for ustekinumab at week 12. PASI 75 data as a function of exposure quantiles; observed (*symbols*) and predicted (*line*) medians with 95% CI (*shaded*). (Adapted from FDA 2008)

Table 17.3 Predicted response rates for ustekinumab under different dosing regimens based on the PASI75-ER model. (Adapted from FDA 2008)

Dosing strategy[a]	Dose	Proposing entity	PASI 75 response predicted from the ER model				
			Overall	By body weight quartiles			
				68 kg	84 kg	96 kg	117 kg
Two tiered	100 kg: 45 mg ≥100 kg: 90 mg	Sponsor	70	77	70	66	69
Three tiered	<60 kg: 45 mg ≥60 kg– 90 kg: 67.5 mg ≥90 kg: 90 mg	FDA	74	79	75	73	69

[a] ER model proposed by the FDA

17.4.2 Facilitating Decision Making Regarding Dose Progression to Phase 3

Pharmacometric methods can support different milestones during drug development to facilitate decision making with respect to trial design, go/no-go decisions, dose selection, and product positioning. The following section illustrates an

example where modeling and simulation were used to develop a probabilistic decision criterion for a safety laboratory endpoint to facilitate phase-3 dose selection for tofacitinib, a novel oral Janus kinase (JAK) inhibitor, currently in development for the treatment of autoimmune conditions such as psoriasis, ankylosing spondylitis, Crohn's disease, etc. Tofacitinib was recently approved for the treatment of adult patients with moderately to severely active rheumatoid arthritis (Xeljanz®).

This example is based on a 12-week phase 2b dose-ranging study evaluating tofacitinib placebo, 2, 5, and 15 mg BID in patients with moderate to severe chronic plaque psoriasis. Phase 3 dose selection was based on the probability of achieving a clinically meaningful target effect (PTE) for the selected laboratory safety and efficacy (data not shown) endpoints (Gupta et al. 2012). PTE calculation took into consideration the clinical meaningfulness of the target effect and the desired confidence in its magnitude as well as the uncertainty associated with the ER relationship(s). Doses were ranked for their performance on the PTE scale; doses achieving a 50% or higher probability were progressed for phase-3 evaluation.

Incidence of hemoglobin drop from baseline was regarded as a clinically relevant laboratory endpoint for model-based assessment. The target effect was set at a placebo-adjusted incidence rate of less than 5% for a hemoglobin change of >2 g/dL decrease from baseline through 12 weeks of treatment. The incidence of hemoglobin drop was predicted from a longitudinal, ER model for this endpoint (Gupta et al. 2012). Modeling hemoglobin levels as opposed to incidence rates offered several advantages: (a) Incidence rates were very small in the studied population and may not have allowed for dose interpolation and (b) characterizing the exposure- and time-dependent trajectories of hemoglobin levels in psoriasis patients offered greater flexibility in predicting the incidence for a trail design of interest.

An indirect response model (with stimulation of elimination (K_{out})) best described the hemoglobin time course across the studied doses. The model was used for predicting the incidence rate of >2 g/dL decrease in hemoglobin. The probability scale for the achievement of target effects was constructed and applied to identify an optimal dose range for phase-3 evaluation. Based on the PTE assessment, 5 and 10 mg BID were selected for phase 3 as they yielded PTE values of 100 and 87%, respectively (Fig. 17.3). This selection was also supported by efficacy considerations which have not been discussed here.

17.5 Integrating Knowledge from Different Sources

A very important component of pharmacometrics is integrating knowledge from other sources such as competitors and/or standard of care to inform strategy and support clinical decisions during a compound's development. Analyses of collective data across multiple studies for other drugs or therapies can provide a quantitative contextualization framework for benchmarking a compound's performance against existing treatment modalities. Prior data for the investigational drug can be used in conjunction with data available in the public domain (e.g., publications in

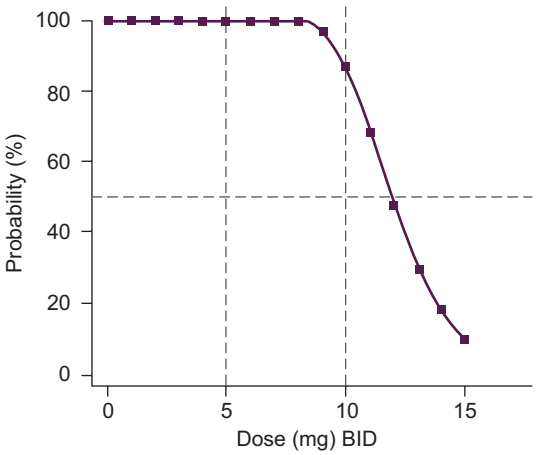

Fig. 17.3 PTE for hemoglobin change for the dose range evaluated in the phase 2b study. P (Incidence of Hgb reduction of > 2 g/dL (placebo adjusted) < 5 %). (Adapted from Gupta et al. 2012)

peer-reviewed journals, summary basis of approvals, conference posters, and abstracts, etc.) for other drugs to make a comparative assessment of the safety and efficacy profiles. Such an integrated evaluation can be further utilized to guide regulatory and commercial strategy.

17.5.1 Meta-Analysis

Meta-analysis is a method of integrating information (summary level data) from different sources to enable indirect comparisons of available treatments. Since very few clinical studies in dermatologic drug development, have undertaken a head-to-head comparison of different treatments in a randomized-controlled setting, this methodology can provide useful information regarding their comparative performance. Meta-analyses evaluating the efficacy of biologic agents in patients with chronic plaque psoriasis have been published in recent years. Most recently, Reich et al. (2012) used a network meta-analysis approach to derive the ranking of biologics, approved in Europe for the treatment of moderate to severe psoriasis (infliximab, etanercept, adalimumab, ustekinumab, and efalizumab). The analysis based on the PASI 50, 75, and 90 response rates was conducted on an ordered probit scale using a Bayesian hierarchical model. The analysis assumed consistency of treatment effects across trials (on a probit scale) and yielded the predicted ranking of different treatments based on probability of achieving the desired PASI response as well as relative risk with respect to placebo. The analysis used data from 20 trials and revealed that infliximab was the most effective treatment followed by ustekinumab, adalimumab, etanercept, and efalizumab.

Another example illustrating the successful utilization of a meta-analytic approach to answer questions pertaining to clinical usage of available atopic dermatitis treatments was reported by Sher et al. (2012). The objective of the analysis

was to compare systemic and topical therapies for their ability to reduce the pruritus associated with atopic dermatitis and to contrast these treatments against their respective controls, i.e., vehicle and placebo for topical and systemic therapies, respectively. The analysis database consisted of 42 studies (representing 7011 patients) for the topical treatment and 10 studies (representing 647 patients) for the oral treatment. An inverse variance fixed-effects model showed that after adjusting for their respective controls, topical treatments were more effective than systemic treatments. Within the topicals, calcineurin inhibitors were found to be more effective than corticosteroids. Among the systemic treatments, data deficiency prevented an evaluation of the effectiveness of antihistamines. However, immunosuppressants were found to be clinically beneficial in reducing pruritus symptoms.

17.5.2 Model-Based Meta-Analysis

Meta-analysis can also be conducted by assuming parametric regression-based models to describe the relationship between exposure (and/or time) and response. Such an analysis termed as model-based meta-analysis (MBMA) may involve assessment at a specified time point (landmark analysis) or utilize data collected over multiple time points (longitudinal analysis). The main advantage of this approach over traditional meta-analysis is the inclusion of all available data (e.g., dose levels) which may increase the precision of the estimated treatment effect (Mandema et al. 2011). Additionally, the impact of differences in patient populations on the treatment effect may be captured quantitatively by virtue of covariate models (Mandema et al. 2011). Finally, MBMA allows for prediction and simulation of data scenarios which may lend themselves quite useful towards optimizing the design of a new study. Such value additions include but are not limited to formulating criteria for proof of concept studies and design elements such as study duration, choice of an active comparator, dose levels, etc.

MBMA may be driven by a specific question of interest. For instance, Janiczek-Dolphin et al. (2010) evaluated the steady state relationship between sebum excretion and acne outcome (measures: total lesion count, acne severity grade, and inflammatory lesion count) using data from multiple studies for acne treatment. The objective of the analysis was to quantitatively characterize this relationship and assess the ability of sebum reduction in predicting acne outcome across various drug classes (retinoid, oral contraceptive, 5-lipooxygenase inhibitor, and oral contraceptive containing antiandrogen) representing patients with mild-moderate to severe disease. Both hyperbolic (E_{max}) and linear (slope–intercept) models were explored, with the latter better describing the effect (E) i.e. acne outcome as a function of reduction in sebum excretion (RSE)

The equation below shows the model used and Fig. 17.4 shows the results for the linear relationship:

$$E = baseline + slope * RSE + \varepsilon / \sqrt{N},$$

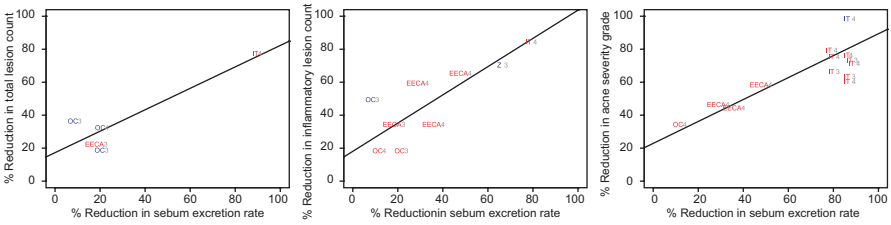

Fig. 17.4 Relationship between sebum reduction and acne outcome measures. Data points represent mean values for a treatment group in an individual study and the *line* represents the model fit. Drug class is shown by *symbols* (*OC* oral contraceptive, *IT* isotretinoin, *EECA* ethinyl estradiol/cyproterone acetate, *Z* zileuton) and duration of treatment for each data point. (Adapted from Janiczek-Dolphin et al. 2010)

where ε is the additive residual error normalized with respect to the number of patients (N).

The model used the totality of available evidence across different drug classes to quantify the association between sebum reduction and acne outcome. This relationship was used to predict the magnitude of sebum reduction required for a certain target improvement in acne outcome measures. The predicted sebum reduction to achieve a 50% improvement in total lesion count, inflammatory lesion count, and acne severity grade was (%, 95% CI): 50.3 (37.8, 75.3), 37.3 (26.6, 62.7), and 40.8 (31.4, 58.0), respectively.

This example clearly illustrates how the application of a simple model involving multiple drugs/classes allowed the quantification of the biomarker-clinical outcome relationship. The learnings from this analysis can prove useful for the development of other treatments for this indication.

17.6 Establishing Bioequivalence of Topical Corticosteroids

Bioequivalence is defined as the lack of a difference in the rate and extent of absorption between a test and a reference formulation. Typically, clinical studies that measure the drug concentration in a reference fluid (e.g., blood, urine) in healthy individuals are performed to compare these product attributes. However, for topical corticosteroid drug products, the FDA permits the use of pharmacodynamic (PD) approaches in order to establish bioequivalence (FDA 1998). The PD-based methodology relies on the vasoconstriction-induced blanching caused by topical dermatologic corticosteroids, which is known to be correlated with their potency, delivery through the stratum corneum and efficacy (Wiedersberg et al. 2008). The FDA guidance document recommends a two-stage approach for bioequivalence assessment. In the first step, a pilot study is conducted to evaluate the dose–response relationship for the corticosteroid followed by a pivotal in vivo study to compare the test and reference product for bioequivalence.

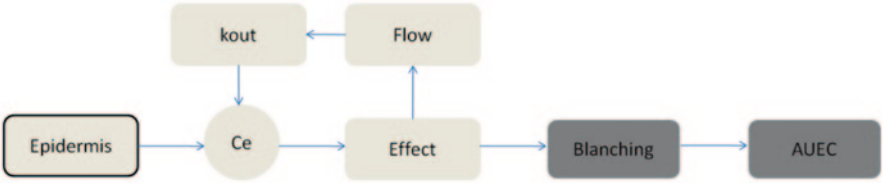

Fig. 17.5 Dermal absorption model for corticosteroids. (Adapted with permission from Holford et al. 2005).

The pilot study involves topical application of the corticosteroid for differing durations. A dose–response curve is constructed based on the increasing duration of exposure to the skin, which can be characterized by an E_{max} model that relates the area under the effect curve (AUEC) and the dose duration (effect is measured as the blanching response). The parameter ED50 reflects the dose duration that produces 50% of the maximum effect (E_{max}). The FDA guidance recommends the use of nonlinear mixed effect modeling or naïve-pooling method for model parameter estimation. The guidance suggests that the bioequivalence testing be carried out at the approximate population estimate of ED50 with two additional dose levels (durations) as half and twice ED50, respectively, also included in the assessment.

The FDA guidance was evaluated by virtue of an exploratory dose–response study comparing six dermatologic corticosteroid creams: 0.05% clobetasol propionate, 0.05% flucinonide-E, 0.5% triamcinolone acetonide, 0.1% betamethasone valerate, 0.05% alclometasonedipropionate, and 2.5% hydrocortisone (potency class: I, III, IV, V, VI, and VII, respectively; Singh et al. 1999). Incremental dosing durations (0.5–6 h) of each drug product were studied for their vasoconstrictive effect (skin blanching). Dose duration–AUEC(0–24) relationship was described by a population E_{max} model for five of the six products (except hydrocortisone) and ED50 values were estimated. Based on this study and analyzing data from a separate bioequivalence study for a potency class III product, it was concluded that the estimated application duration (ED50) provided an appropriate dose for designing the pivotal bioequivalence study.

Holford et al. (2005) challenged these findings and the agency recommendation by employing a modeling and simulation approach. The authors proposed a semi-physiological model to describe dermal absorption characteristics of corticosteroids (Fig. 17.5). In this model, drug delivery to the epidermis occurred at a constant rate (input = rate*extent); drug loss from the epidermis was a first order process governed by the rate constant k. The equation below describes the instantaneous change in drug levels "*E*" in the epidermis:

$$\frac{d\ E}{dt} = input\ -\ k.E.$$

The effective drug concentration (*C*e) which produces vasoconstriction is a function of blood flow:

$$\frac{d\ Ce}{dt} = k.E - Flow * Eff\ * \frac{Ce}{Ve}$$

$$Eff = 1 - E_{max} * \frac{Ce}{EC50 + Ce},$$

where *Flow* refers to the blood flow, *Eff* is the drug effect and *V*e is the volume of the effect compartment. Time course of skin blanching is a function of vasoconstriction produced by the corticosteroid.

AUEC was calculated by integrating the blanching effect over the period of application. The simulation study showed AUEC was not a robust measure under scenarios of rapid absorption thus suggesting that the choice of ED50 as an anchoring point for design may not always be justifiable.

As an alternative to the vasoconstrictive assay, microdialysis and dermatopharmamacokinetic (DPK) approaches have also been proposed as effective methods for BE assessment (Wiedersberg et al. 2008). The former technique has been discussed earlier; DPK involves drug extraction from the stratum corneum by virtue of repeated tape stripping and works best for quantifying the delivery of drugs such as antifungals, keratolytics, and antiseptics that act primarily in the stratum corneum (Wiedersberg et al. 2008).

17.7 Summary

- Dermatologic drug development can benefit tremendously from the advancement in pharmacometrics methods.
- As has been discussed in this chapter, the application of these methods can impart efficiencies at different junctures in development by reducing the uncertainty in the efficacy and safety profiles of the drug candidate and facilitating the progression along the development continuum.
- Ultimately, pharmacometrics techniques can provide the necessary framework for an objective evaluation of benefits versus risks with the intent of providing optimal therapy to the target patient population.

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