Chapter 16
Pharmacometric Applications in Inflammation

Sujatha Menon and Sriram Krishnaswami

16.1 Introduction

A comprehensive list of inflammatory conditions would comprise over hundred diseases, including Alzheimer's disease, ankylosing spondylitis (AS), arthritis (osteoarthritis, OA, rheumatoid arthritis, RA, psoriatic arthritis, PsA), asthma, atherosclerosis, Crohn's disease, colitis, dermatitis, diverticulitis, fibromyalgia, hepatitis, irritable bowel syndrome (IBS), systemic lupus erythematosus (SLE), nephritis, Parkinson's disease (PD), ulcerative colitis, etc. (List of inflammatory diseases 2013) A brief review of the literature suggests that there are numerous successful and ongoing pharmacometric endeavors in many of these diseases. Pharmacometric applications to neurodegenerative disorders, such as Alzheimer's disease and PD, are discussed elsewhere as are applications to diseases, such as plaque psoriasis, in the dermatology area.

Numerous mathematical models have been developed to describe the disease progression and effects of anti-inflammatory drugs (Lon et al. 2012). In the excellent review by Lon et al. (2012), the authors illustrate the state of the art in modeling the effects of diverse drugs for treating inflammation, describe relevant biomarkers amenable to modeling, and summarize major advantages and limitations of the published pharmacokinetic/pharmacodynamic (PK/PD) models. The authors review the development of models ranging from direct inhibitory models to indirect response models to characterize symptoms and biomarkers. Target-mediated and transduction models as well as systems pharmacology models have been successfully applied to capture the PK/PD of many anti-inflammatory drugs and describe disease progression of inflammation. In addition, biologic treatments offer opportunities to develop different types of models due to their specific mechanisms of action, such as neutralization of specific cytokines, elimination of specific immune cells, blockade of costimulation for T-cell activation, and inhibition of cell adhesion (Lon et al. 2012). Small systems models have also been developed to describe bone formation

S. Krishnaswami (✉) · S. Menon
Department of Clinical Pharmacology, Pfizer, Groton, CT, USA
e-mail: Sriram.Krishnaswami@pfizer.com

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and resorption using biomarkers as well as clinical outcomes such as bone mineral density (Lemaire et al. 2004; Marathe et al. 2008, 2011; Schmidt et al. 2011).

Apart from PK/PD/disease models, large-scale systems biology models have also been developed, ranging from those describing the underlying disease process (inflammation and erosion of joints) in patients with RA (Rullmann et al. 2005) to bone homeostasis models (Peterson and Riggs 2010) to those that combine the strategies of systems biology and network pharmacology to investigate multi-targeted mechanisms of traditional Chinese medicine (Zhang et al. 2013).

Given this background, we have attempted to focus on a few documented applications in optimizing drug development strategy and/or regulatory approval. The selected case studies are by no means comprehensive or a reflection of the most influential or impactful endeavors because many successful applications are likely not in the public domain. Instead, the examples highlight some key learnings that should be broadly applicable in drug development decision making. In addition, an attempt has been made to provide a comprehensive reference list of various pharmacometric endeavors in this multifaceted therapeutic area.

16.2 Case Studies

16.2.1 Decision to Terminate Clinical Development of Canakinumab for the Treatment of RA (Demin et al. 2012)

Canakinumab (ACZ885) is a fully human monoclonal antibody that suppresses IL-1β-mediated joint inflammation and cartilage destruction in mice. A successful proof-of-concept (POC) study in patients with RA triggered a decision to conduct a dose-finding study. The key question was whether the magnitude of efficacy was sufficiently robust to warrant progression to a large phase 3 development program, which typically costs several hundreds of millions.

RA is an autoimmune disease that leads to inflammation, progressive joint damage, and disability. It affects ~1% of adults worldwide, predominantly women. Advances in understanding the pathogenesis of this highly heterogeneous disease have fostered the development of several new therapeutics with vastly improved outcomes over the past decade. Numerous cytokines, growth and differentiation factors, and intracellular signaling molecules and transcription factors have been implicated in the pathogenesis of RA (Table 16.1). However, to date, there are no reliable predictive biomarkers of prognosis, therapeutic response, or toxicities such as increased mortality, cardiovascular, and other systemic complications of the disease.

Current international treatment recommendations for the management of RA state that the treatment of RA should be aimed at reaching a target of remission or low disease activity as soon as possible in every patient; and as long as the target has not been reached, treatment should be adjusted by strict monitoring every 1–3 months (Smolen et al. 2010). Methotrexate (MTX) is part of the first treatment strategy in

Table 16.1 Key molecules and signal mediators implicated in the pathogenesis of rheumatoid arthritis

Molecule or signal mediator	Key disease relevant functions	Status[a]
Cytokines		
TNF-α	Activates leukocytes, endothelial cells, and synovial fibroblasts, inducing production of cytokines, chemokines, adhesion molecules, and matrix enzymes; suppression of regulatory T-cell function; activation of osteoclasts; and resorption of cartilage and bone; mediates metabolic and cognitive dysfunction	Approved drug
Interleukin-1α and 1β	Activate leukocytes, endothelial cells, and synovial fibroblasts; induce matrix-enzyme production by chondrocytes; activate osteoclasts; mediate fever; enhance glucose metabolism; and reduce cognitive function	Approved drug
Interleukin-6	Activates leukocytes and osteoclasts; is involved in B-lymphocyte differentiation; regulates lipid metabolism, acute-phase response, and anemia of chronic disease; and is implicated in hypothalamic–pituitary–adrenal axis dysfunction and fatigue	Approved drug
Interleukin-7 and 15	Promote and maintain T-cell and natural killer–cell activation and T-cell memory, block apoptosis, and maintain T-cell–macrophage cognate interactions	Phase 2 trial completed
Interleukin-17A and 17F	Act synergistically to enhance activation of synovial fibroblasts, chondrocytes, and osteoclasts	More than one phase 2 trial with positive results
Interleukin-18	Promotes activation of Th1, neutrophils, and natural killer cells	
Interleukin-21	Activates Th17 and B-cell subsets	
Interleukin-23	Expands Th17	
Interleukin-32	Activates cytokine production by several leukocytes and promotes osteoclast differentiation	
Interleukin-33	Activates mast cells and neutrophils	
Growth and differentiation factors		
BLyS and APRIL	Activate B cells and have a role in the maturation of B cells and enhancement of autoantibody production	In phase 2 trial

Table 16.1 (continued)

Molecule or signal mediator	Key disease relevant functions	Status[a]
GM-CSF and M-CSF	Enhance differentiation of granulocyte and myeloid-lineage cells in the bone marrow and synovium	In phase 1 trial
RANKL	Promotes maturation and activation of osteoclasts	Phase 2 trial completed
Intracellular signaling molecules and transcription factors		
JAK	Tyrosine kinase that regulates cytokine-mediated leukocyte maturation and activation, cytokine production, and immunoglobulin production	Approved drug
Syk	Tyrosine kinase that regulates immune-complex–mediated and antigen-mediated activation of B and T cells and other Fc receptor-bearing leukocytes	More than one phase 2 trial with positive results
PI3K	Mediates signals that drive proliferation and cell survival	Phase 1 trial planned
BTK	Plays an important role in the activation of B cells, macrophages, mast cells, and neutrophils, through regulation of B-cell receptor and Fc receptor signaling as appropriate	Phase 1 trial planned
NF-κB	Helps integrate inflammatory signaling and is important for cell survival	

APRIL a proliferation-inducing ligand, *BLyS* B-lymphocyte stimulator, *BTK* Bruton's tyrosine kinase, *GM-CSF* granulocyte–macrophage colony-stimulating factor, *JAK* Janus kinase, *M-CSF* macrophage colony-stimulating factor, *PI3K* phosphatidylinositol 3-kinase, *RANKL* receptor activator of NF-κB ligand, *Syk* spleen tyrosine kinase, *Th1* type 1 helper T cells

[a] Status indicates the investigational status of agents targeting the molecule or signal mediator. Approved drugs have been approved by the Food and Drug Administration and European Medicines Agency for use in patients with rheumatoid arthritis. Trials are clinical trials that are ongoing or have been completed. Reproduced with permission from McInnes and Schett (2011)

patients with active RA. However, the majority of patients experience an inadequate response to a therapeutic intervention with MTX, and many are treated with at least two nonbiologic disease-modifying antirheumatic drugs (DMARDs) before receiving a tumor necrosis factor inhibitor (TNFi). The remaining patients are treated with a biologic DMARD, especially a TNFi, typically administered in combination with MTX, which is now the standard of care (SOC). Often one or more TNFis are prescribed, but ultimately many patients move to biologic DMARDs with other mechanisms of action, and medical needs are not fully met for many patients. Thus, there remains an unmet medical need for additional therapeutic options with unique mechanisms of action, proven efficacy, and acceptable safety profiles in patients with moderate-to-severe active RA.

A systematic review of the published literature on clinical trials of biological treatments in RA was performed, using processes that have been previously

described (McDevitt et al. 2009). The majority of the trials were placebo controlled; in one trial (Schiff et al. 2008), a head-to-head comparison of two biologics (abatacept and infliximab) was performed. For the purposes of the meta-analysis, only data on approved doses and regimens were retained.

This integrated analysis included data from 37 phase 2–3 studies describing 13,474 patients. The primary end point for decision was the American College of Rheumatology (ACR)20 responder rate, which is the percentage of patients who responded to the relevant criterion based on improvements in tender or swollen joint counts and improvement in three of the following five parameters: acute phase reactant (such as sedimentation rate), patient assessment physician assessment, pain scale, and disability/functional questionnaire. Since nearly all published pivotal trials use this measure of efficacy, it provides for a standardized way to compare treatments. However, as would be expected, the ACR end point is limited by reduced precision compared to a continuous measure such as disease activity score. The final nonlinear mixed-effects model used for fitting ACR20 time course data was:

$$\text{logit}(y_{ilj}) = \text{logit}\left(\frac{\tilde{\phi}_{1k} t_{ij}^{\gamma_m \alpha}}{\exp(\theta_{2k_2})^{\gamma_m} + t_{ij}^{\gamma_m}}\right) + \varepsilon_{ilj}$$

$$\tilde{\phi}_{1k} = M\left(\frac{\exp(\phi_{1k})}{1+\exp(\phi_{1k})}\right), \quad \phi_{1k} = \theta_{1k} + \eta_{1i} + \eta_{2il},$$

$$\eta_{1i} \sim N(0, \omega_1^2), \quad \eta_{2il} \sim N\left(0, \frac{\omega_2^2}{N_{il}}\right), \quad \varepsilon_{ilj} \sim N\left(0, \frac{\sigma^2}{N_{il}}\right),$$

where i is the index over studies, l is the index for treatment arm within a study, and j is the index over time within a study. The index k represents therapies, and k_2 represents drugs. Two different γ_m values were estimated: one for biologics and one for placebo-plus-MTX and true placebo ($m=1, 2$). The E_{max} parameter $\varphi_{1,k}$ is logit transformed with $M=100$ for all treatments except certolizumab and infliximab (drugs with decreasing response at later time points), for which $M=300$. The fixed-effects θ_{1k} values represent E_{max} parameters, and fixed-effects θ_{2k2} values are time course parameters. The offset of the effect parameter α is set at 1 for all treatments except certolizumab and infliximab, for both of which $\alpha<1$. Random-effects parameters $\eta 1_i$ and $\eta 2_{il}$ represent between study variability (BSV) and between treatment arms variability (BTAV), respectively. Residual unexplained variability, ε_{ilj}, and BTAV, $\eta 2_{il}$, are adjusted according to the number of subjects in a treatment arm. The model was implemented in a Bayesian framework and coded in WinBUGS.

Figure 16.1 shows the model-based predictions of the time course of ACR20 responder rates for canakinumab in comparison to SOC treatments, etanercept and adalimumab, as well as placebo. It showed that, with the tested doses/regimens of canakinumab, there was only a low probability that this drug would be better than the most effective current treatments. At the most effective dose, the analysis predicted a very low probability (<3%) of canakinumab being better than certolizumab or infliximab, and 8% probability of being better than adalimumab, per ACR20

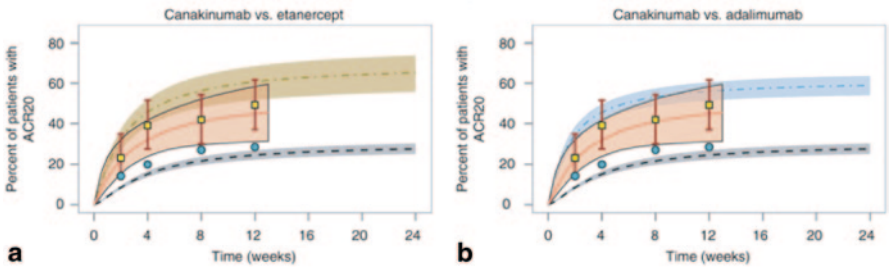

Fig. 16.1 Model-based comparison of ACR20 responder rates for canakinumab versus placebo and SOC treatments, etanercept and adalimumab. Canakinumab (both panels, *red solid lines*), etanercept (panel **a**, *brown dash-and-dot line*), adalimumab (panel **b**, *blue dash-and-dot line*), and placebo (both panels, *gray broken lines*). *Blue circles* represent placebo-plus-MTX data from the canakinumab study. *Yellow squares* represent the observed ACR20 values (with *red vertical bars* for 95% confidence intervals) for canakinumab. The shaded areas are the respective 90% Bayesian confidence intervals for model-based predictions. (Reproduced with permission from Demin et al. 2012, CPT)

scores after 12 weeks of treatment. This finding supported the decision not to continue with clinical development of canakinumab in RA.

16.2.2 Decision to Expand the Size and Scope of a Dose-Finding Study and Using Benefit and Risk Data to Select Doses for Phase 3 Testing. (Milligan et al. 2013)

This example illustrates the prospective application of model-based drug development (MBDD) concepts to the late-stage development of tofacitinib, a potent immunomodulator with a novel mechanism of action, for the treatment of RA. Results from a POC trial demonstrated a high degree of efficacy but with side effects. The challenge was to identify dose(s) of this orally administered, small molecule for pivotal registration trials that would achieve a minimally acceptable product profile of similar efficacy as biologic injectables, with acceptable safety.

Tofacitinib is a Janus kinase (JAK) inhibitor. JAK enzymes transmit the signaling of several pro-inflammatory cytokines involved in the pathogenesis of RA through pairings of JAKs (e.g., JAK1/JAK3, JAK1/JAK2) and tofacitinib works by inhibiting the activities of these combinations, resulting in modulation of cellular processes of hematopoiesis and immune cell function.

The first evidence of efficacy in RA patients was observed in a 6-week POC study of 5, 15, and 30-mg twice-daily (BID) doses of tofacitinib and placebo (Kremer et al. 2009). All doses demonstrated efficacy as measured by the ACR response criteria but were also associated with side effects, such as dose-dependent changes in laboratory markers (e.g., decreased neutrophils). The challenge was to efficiently yet comprehensively characterize dose-response relationships to identify optimal dose(s) for confirmatory trials. This process began by gaining agreement with stakeholders on the key questions and setting quantitative and action-oriented objectives for the phase 2b program, as illustrated below (Sheiner 1997).

What do we need to know? Identify the lowest dose with at least 30% difference in ACR20 response versus placebo by week 12. ACR20 response was chosen because it was the primary efficacy end point in the study to demonstrate superiority to placebo. However, the operating characteristics of the study were also verified to be reasonable with respect to ACR50 and ACR70 end points.

How sure do we want to be? Desire 80% probability that the true response for the model-estimated dose will be within ±20% of the target efficacy magnitude, i.e., 24–36%.

What are we willing to assume? A pharmacologically based, longitudinal E_{max} model will be applied; the dose range derived from the monotherapy POC study data will be applicable to combination treatment with MTX; priors for the model-based analysis will be weakly informed by the POC study data.

Various longitudinal, dose–response models were developed, including an indirect latent variable response model, relating pharmacologically based models to categorical data (Hutmacher et al. 2008). The various models gave similar predictions of the data but showed differences in their predictive performance when extrapolating to lower doses and later time points. Consequently, they were used as "data-generation" models to ensure that the design chosen had robust operating characteristics over a range of "true" relationships (Krishnaswami et al. 2009). A similar approach was implemented to characterize decreases in absolute neutrophil counts. Since the neutropenia incidence data from the POC study were too sparse, modeling efforts were focused on characterizing neutrophil counts using indirect response and semi-mechanistic models (Gupta et al. 2010) to provide a more stable basis for dose and time interpolation/extrapolation. Using clinical trial simulations, it was determined that the 10th percentile of the neutrophil count distribution was related to the risk of neutropenia and estimated with greater precision than the neutropenia incidence data, thereby providing an efficient way to eliminate doses with unacceptable neutropenia event rates predicted based on changes in continuous data.

Two 6-month, phase 2b studies were performed in which tofacitinib was administered either as monotherapy (Fleischmann et al. 2012) or in combination with MTX (Kremer et al. 2012). Both studies evaluated placebo and tofacitinib doses of 1, 3, 5, 10 and 15 mg BID. The sample sizes of these studies, totaling > 800 patients, were larger than traditional phase 2 sample sizes because they were designed to support quantitative decision criteria aimed at identifying an optimal dose rather than statistical separation from placebo. Traditional pairwise comparisons would have necessitated a 70% increase in study size (approximately 1300 patients) to achieve similar performance characteristics over a model-based approach.

Model-derived inferences, updated using Bayesian methods, were used to calculate the probability of technical success, i.e., the probability of achieving efficacy similar to that of SOC TNF inhibitor treatment (Tan et al. 2011; Tofacitinib FDA Advisory Meeting 2012). As predicted from the POC study, changes in neutrophils and predicted incidence of neutropenia were within acceptable limits and, therefore, not considered to limit the dose range under consideration for phase 3 trials. However, dose-dependent changes in hemoglobin levels were noted. A longitudinal model was applied to capture the relationship between dose and hemoglobin levels. An empirical model was applied to capture the apparent inverted U-shaped

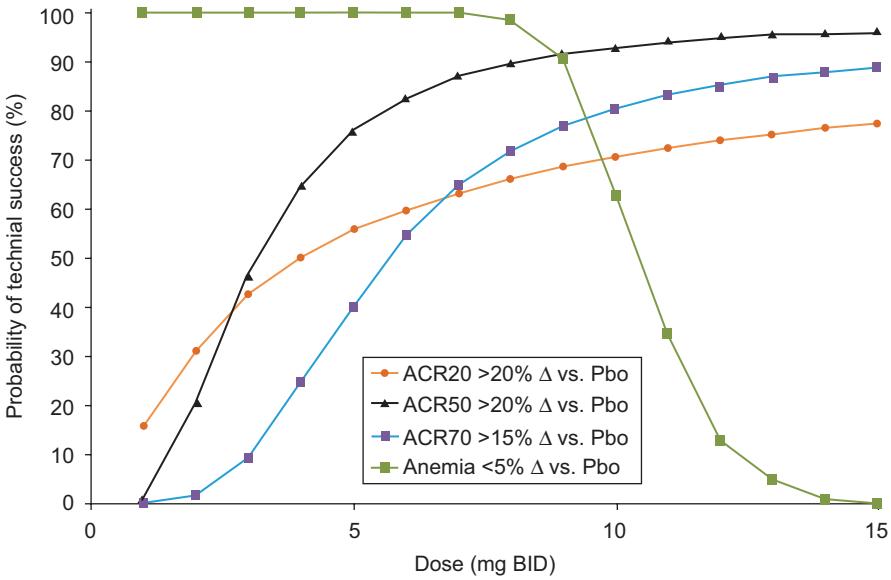

Fig. 16.2 Tofacitinib—probability of achieving targeted differences versus placebo. *Solid symbols* and *lines* represent model-based probability estimates for ACR responses and anemia. *ACR* American College of Rheumatology, *Pbo* placebo. (Reproduced with permission from Milligan et al. 2013)

relationship between dose and hemoglobin levels, possibly arising out of beneficial effects (improvement in the anemia associated with chronic disease, i.e., active RA) at lower doses and a combination of beneficial and deleterious effects (potentially due to JAK2 inhibition) at higher doses. The probability that the incidence of clinically important anemia (defined as >2 g/dl decreases from baseline in hemoglobin or absolute value <8 g/dl) will not exceed 5% above placebo over 6 months of treatment was calculated. As shown in Fig. 16.2, modeling based on the MTX combination study predicted that doses from 5 to 10 mg BID inclusive would meet both the desired efficacy and safety criteria of having approximately 50% or greater probability of achieving efficacy similar to SOC, with anemia rates <5% above placebo. In contrast, a 3-mg dose had a 10% chance of achieving the ACR70 target compared to 40% for the 5-mg dose. It is noteworthy that while the MTX combination study was designed to identify a dose that produced at least 30% difference in ACR20 rates from placebo, none of the doses in this study actually showed differences >30%, attributable to an unexpectedly high placebo rate (>40%). On the other hand, ACR50 and ACR70 response rates from the study encompassed a range of responses typically associated with TNF inhibitor treatment. As a consequence, the acceptance criteria for ACR 20 dose selection was modified to at least a 20% difference from placebo to provide better discrimination of doses between 1- and 15-mg dose range while the original criteria was retained for ACR50 and ACR70 rates.

The choice of 5- and 10-mg doses was independently verified in the monotherapy phase 2b study which became available after phase-3 dose selection was made

based on the MTX combination study. This study monotherapy showed that doses ≥5 mg provided the requisite level of efficacy, including >30% differences in ACR 20 rates from placebo, whereas a 3-mg dose was considered clinically suboptimal, even though it separated from placebo (Fleischmann et al. 2012). Thus, the totality of the data justified the choice of 5- and 10-mg BID doses for phase 3 studies.

The results from the phase 3 program were consistent with these model predictions. The efficacy of 5 mg BID was as predicted (29% difference in ACR20 rate vs. placebo across five phase 3 studies) and, more importantly, similar to that of SOC TNF inhibitor treatment (adalimumab; van Vollenhoven et al. 2012a). The rates of anemia and neutropenia were low and considered manageable with appropriate clinical monitoring.

A prospective approach to (a) designing studies to a stringent quantitative criteria, (b) characterizing exposure–response relationships using well-established clinical outcome data in patient populations representative of the phase 3 program, and (c) selecting doses based on efficacy and safety using probability of technical success as a common metric allowed demonstration of a positive benefit: risk profile with the desired product attributes. Tofacitinib 5 mg BID was approved in 2012 by the FDA for the treatment of moderately-to-severely active RA.

16.2.3 Decision to Approve a Pediatric Dose and Formulation Not Tested in a Pivotal Registration Trial (Krishnaswami et al. 2012)

Celecoxib is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities by inhibiting prostaglandin synthesis, primarily via inhibition of cyclooxygenase-2 (COX-2) but not COX-1 at therapeutic concentrations in humans (Gierse et al. 2002). In addition to adult indications, it is currently approved for the treatment of juvenile rheumatoid arthritis (JRA), a group of disorders characterized by idiopathic inflammatory arthritis. The key question during the pediatric development program was whether an alternative dosing scheme supportable by available formulation could be derived from studies that used an investigational formulation to evaluate efficacy, safety, and PK.

Prior to and during the conduct of the efficacy/safety trial in JRA patients (Foeldvari et al. 2009), several attempts were made to develop an age-appropriate pediatric formulation, including oral suspension, orally disintegrating tablets, and chewable tablets. None of these were suitable for commercialization in a timely manner because of technical challenges. Thus, the development team was faced with the conundrum of having efficacy, safety, and PK data, in the pediatric population, but without a commercializable formulation. Thus, the overall objective of this pharmacometric endeavor was to bridge data across formulations, methods of administration, and populations to derive dosing recommendations for JRA patients. This was achieved in three steps: (1) assessing exposures in JRA and adult RA patients administered celecoxib suspension (i.e., formulation used in the efficacy trial)

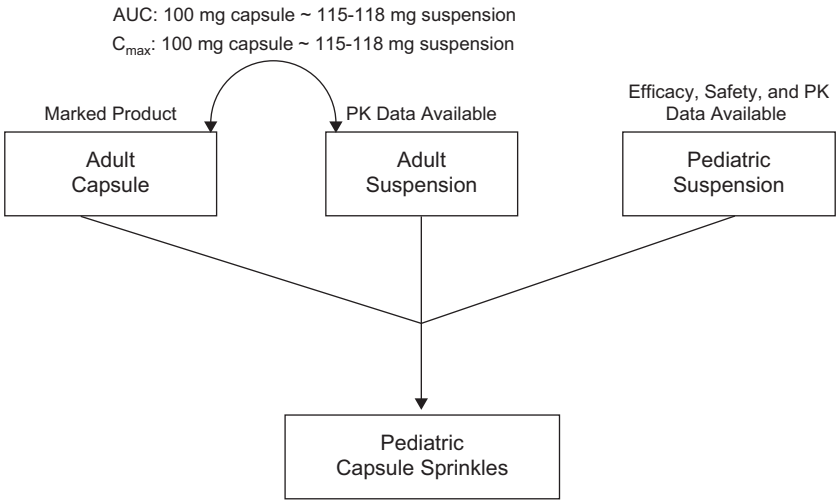

Fig. 16.3 Bridging strategy for celecoxib sprinkles in patients with JRA. (Reproduced with permission from Krishnaswami et al. 2012)

and characterizing the PK/PD relationship, (2) comparing the suspension exposures to capsule (marketed formulation) exposures, and (3) evaluating the suitability of administering celecoxib capsules as sprinkles (on applesauce) for those who may be unable or unwilling to swallow an intact capsule (Fig. 16.3).

A complicating factor in bridging capsule and suspension was that although similar AUC was expected between the two dosage forms at the same doses, C_{max} would be higher (approximately doubled) for the capsule formulation. Therefore, the rationale for the selection of capsule doses was based on achieving concentrations that do not exceed those observed in the JRA trial using the suspension formulation (safety boundary), while achieving similar overall exposures as those shown to be noninferior to naproxen (efficacy boundary), an approved drug for the treatment of JRA. Because two doses (3 and 6 mg/kg BID) of celecoxib suspension were evaluated in the efficacy trial and both were found to be noninferior to naproxen 7.5 mg/kg BID and well tolerated (Foeldvari et al. 2009), concentrations in between those of the two dose groups were targeted. The prediction of pediatric capsule PK profiles was made by combining historical capsule parameter estimates in adults and the estimated power exponents for the effect of weight on CL/F and V/F in the JRA efficacy trial. It was fortuitous that the power exponent for the weight effect on CL/F was 0.265 ± 0.074, resulting in typical oral clearance (L/h) values that were only 40 and 24% lower in patients weighing 10 and 25 kg, respectively, compared with a 70-kg patient. This allowed the potential use of a less flexible dosing form (capsule) compared to a liquid formulation.

Mechanistically, whether these results were a true reflection of the weight–clearance relationship or an artifact arising out of possible influence of collinear covariates was evaluated by fixing the weight effect to an allometric model (typical $CL/F = \theta 1 \times [weight_i/41]^{0.75}$; typical $V/F = \theta 2 \times [weight_i/41]$) and estimating the relationship between age and CL/F and age and V/F using centered power

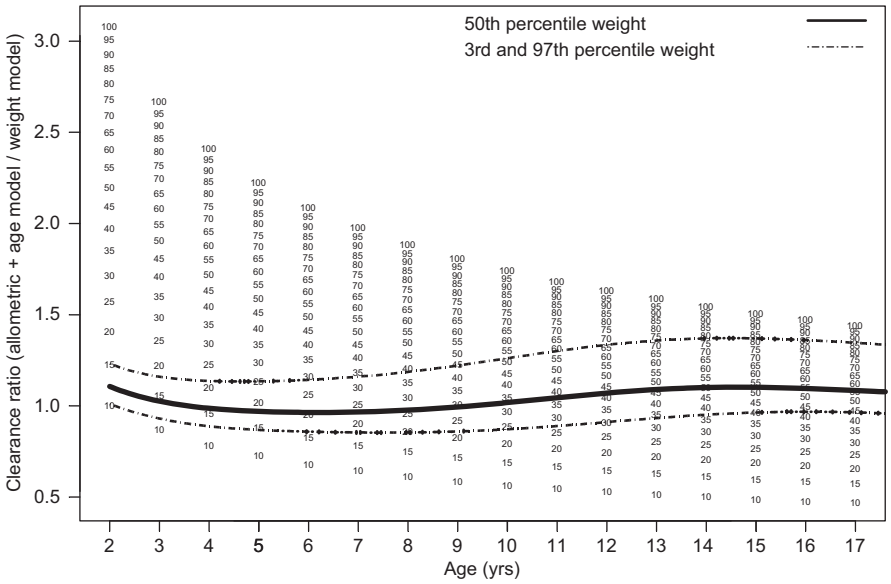

Fig. 16.4 Comparison of typical clearance estimates between allometric-plus-age model and weight-effect model. *Symbols* represent body weight; *lines* represent clearance ratios for 3rd (*lower dotted*), median (*solid*), and 97th (*upper dotted*) percentile body weights by age according to CDC weight chart. (Reproduced with permission from Krishnaswami et al. 2012)

functions. The motivation for choosing age as the second covariate was not based on the plausibility of incomplete maturation of metabolism or excretion processes, because patients typically attain full function by 2 years of age, but rather from a report showing a similar departure from allometry for another anti-inflammatory agent (leflunomide) in the JRA population (Shi et al. 2005).

Recent evidence suggests that inflammation due to underlying infectious or inflammatory conditions is associated with downregulation in the expression of several drug-metabolizing enzymes (Schmith and Foss 2010). This raised the possibility that age could be a surrogate of inflammatory burden (i.e., younger children having a lower burden of disease/inflammation compared with older children, and thus resulting in decreasing oral clearance with increasing age). Although the addition of two such parameters describing the relationship between age and CL/F and age and V/F resulted in only a 6.3-point decrease in the objective function (not statistically significant) relative to the weight-effect model (power exponent = 0.265), the parameters were estimated reasonably well (relative SE < 25 %). This suggests that caution should be exercised in interpreting the weight–clearance relationship from a mechanistic standpoint. However, the model choice or philosophy would not be expected to affect dosing decisions because the estimate of the power exponent in the weight-effect model should reflect a net effect of allometry and age. Indeed, typical clearance values calculated over a range of theoretical age (2–17 years) and weight (10–100 kg) combinations according to the 3rd, 50th, and 97th percentile Centers for Disease Control and Prevention weight charts are mostly similar between the allometric-plus-age model and the weight-effect model (Fig. 16.4). The

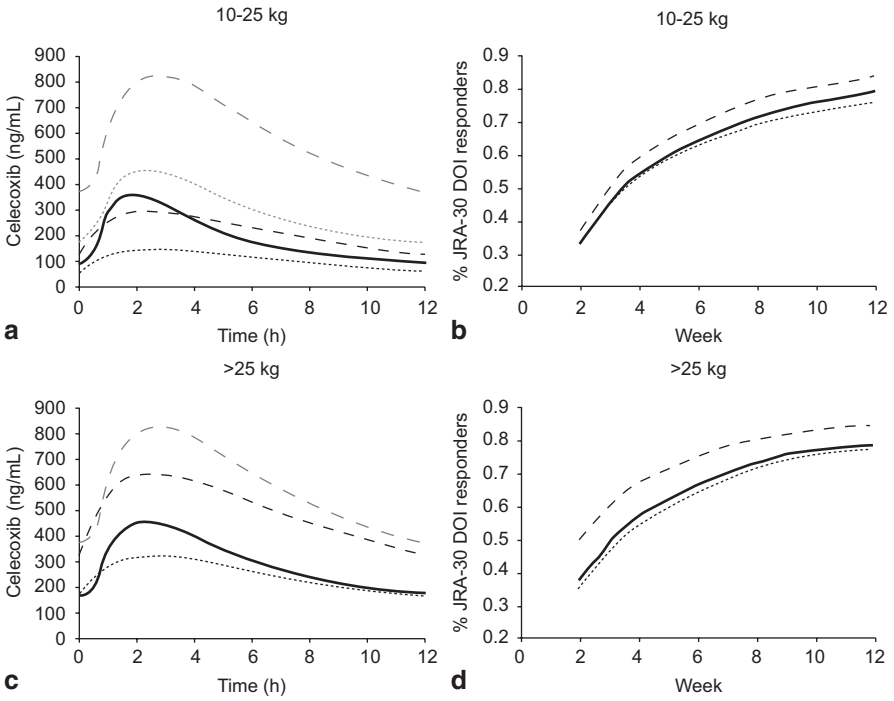

Fig. 16.5. Simulated PK/PD profiles for suspension and capsule dosing schemes of celecoxib in juvenile rheumatoid arthritis (JRA). *Black short* and *long dash lines* represent 3 and 6-mg/kg BID suspension, respectively, in JRA; *black solid line* represents (**a**, **b**) 50-mg bid or (**c**, **d**) 100-mg BID capsule in JRA; gray short and long dash lines represent 100- and 200-mg BID doses of capsule, respectively, in adult rheumatoid arthritis patients. *DOI* definition of improvement. (Reproduced with permission from Krishnaswami et al. 2012)

models diverge only under extreme scenarios (e.g., a 2-year-old child would have to weigh 40 kg to need twice the dose as compared with a 10-year-old weighing 40 kg under the allometric-plus-age model). Moreover, at younger ages, the allometric-plus-age model tends to suggest the need for higher doses under such extreme weight scenarios, making it of less utility in the absence of safety data. Thus, the simpler and more conservative weight-effect model was considered appropriate to derive dosing instructions.

Simulations supported a reduction in the number of weight-based dosing tiers employed in the JRA efficacy trial from five (10–12, 13–25, 26–37, 38–50, and >50 kg) to two (10–25 and >25 kg). An overall summary is shown in Fig. 16.5, where the simulated PK (including historical adult capsule data for reference) and efficacy profiles (percent responders) are depicted for the 10- to 25 and >25-kg weight categories for the suspension doses used in the efficacy study and for the recommended capsule doses. The results are consistent with the approach of achieving efficacy closer to that of the lower dose (3 mg/kg) tested in the efficacy study while ensuring that C_{max}, particularly in lighter patients, is not significantly greater than those of the higher dose (6 mg/kg) tested in the efficacy study (Fig. 16.5).

Finally, the interchangeability of different delivery methods (administration of the commercial capsule intact or as sprinkles) was demonstrated in adults in order to support dosing in children who are unable to swallow intact celecoxib capsules.

16.2.4 Decision to Test Higher Dose Space Based on Knowledge Derived from Totality of Internal and External Data (Kowalski et al. 2008)

SC-75416 is a benzopyran (chromene) COX-2 inhibitor, a novel class of compounds with anti-inflammatory and analgesic activity demonstrated in preclinical models of pain and inflammation. An initial dose-ranging study in post-surgical dental patients indicated that the tested doses of a capsule formulation of SC-75416 did not achieve pain relief (PR) response similar to SOC. PR scores were measured on a 5-point Likert scale (PR = 0: no pain relief; PR = 4: complete pain relief). In addition, patients receiving SC-75416 dropped out of the study and took rescue medication at a higher rate than those receiving the reference standard (rofecoxib 50 mg, currently withdrawn from the market). The key development question was whether the dose range tested was adequate to support compound termination at that point in time, or if there was a rationale to pursue higher doses that would ultimately provide efficacy differentiation from marketed products.

A modeling and simulation strategy was employed to leverage internal and external data from SC-75416, and from other products (rofecoxib, valdecoxib, and ibuprofen) to address this question. Models to characterize PR as well as dropout (time to rescue) were employed based on previously published methodology for the analysis of non-randomly censored ordered categorical data, which is typical of analgesia trials (Sheiner 1994; Mandema and Stanski 1996; Sheiner et al. 1997). A key data piece that shed light on the potential reason for the less-than-expected efficacy was the lower and more variable absorption profile of the capsule formulation of SC-75416 in the first 6 h after dosing in patients with dental pain compared to that of an oral solution (previously evaluated in healthy subjects). To assess the impact of this difference, the PR and dropout models together with the observed PK profile for the oral solution were used to predict the PR score profile for the oral solution formulation. These predictions, which are extrapolations outside of the data generated from the initial dental pain study using capsule, suggested that equivalent doses of the compound administered as an oral solution should provide higher PR response compared to those of the capsule. More importantly, higher doses of the oral solution were predicted to surpass the efficacy of an approved drug (ibuprofen 400 mg). To further increase the confidence to invest in another study to test this hypothesis, particularly to estimate the probability of success relative to ibuprofen, additional PK/PD modeling was performed pooling post-oral surgery pain data from valdecoxib studies where 400-mg ibuprofen had been used as an active comparator. The PR and dropout model parameters estimated were used to obtain two sets of population mean predictions of efficacy for SC-75416 oral solution doses ranging from 30 to 360 mg. An important assumption was made that all of these drugs can

Table 16.2 Comparison of observed and predicted TOTPAR6 responses for the SC-75416 oral solution post-oral surgery pain study. (Reproduced with permission from Kowalski et al. 2008)

Treatment group	T0TPAR6 (mean ± SE)		ΔTOTPARe[a]	
	Predicted[b]	Observed	Predicted[b]	Observed
Placebo	3.9 ± 0.9	1.4 ± 0.6	−7.1	−9.6
60 mg SC-75416	10.1 ± 1.4	9.2 ± 1.2[c]	−0.9	−1.8
180 mg SC-75416	13.0 ± 1.2	13.7 ± 1.2[c]	2	2.7[d]
360 mg SC-75416	14.2 ± 0.9	14.3 ± 0.8[c]	3.2	3.3[d]
400 mg ibuprofen	11.0 ± 0.8	11.0 ± 0.8[c]	0	0

[a] Difference in TOTPAR6 relative to 400 mg ibuprofen
[b] Predicted based on Model IIA/IIB
[c] Significantly different ($P < 0.05$) relative to placebo
[d] Significantly different ($P < 0.05$) relative to ibuprofen

achieve the same maximum drug effect, and differences in effectiveness between the compounds is dependent only on their exposure relative to their potency.

Because different data sources were used to obtain the two sets of population mean predictions of efficacy, considerable discrepancy in the dose–response predictions were noted between the two models. The predicted SC-75416 oral solution dose–response profile based on the single study was steeper compared to that predicted based on the analysis of competitor data. The parameter estimates of the PR and dropout models are less precise for the SC-75416 capsule post-oral surgery pain model because they are based on the results of a single study, and because the SC-75416 treatments had unexpectedly low exposure due to the poor absorption of the capsule formulation. For these reasons, the more conservative predictions based on the post-oral surgery pain modeling of the data from the valdecoxib studies were considered more robust and hence were used in subsequent clinical trial simulations to evaluate designs in planning the SC-75416 oral solution post-oral surgery pain study.

Based on the updated PK/PD and dropout models from the valdecoxib study and the potency (EC50) estimate for SC-75416 from the fit to the SC-75416 capsule post-oral surgery pain study, clinical trial simulations were conducted to evaluate and optimize the study design (doses and sample sizes) for a superiority trial. The design was optimized using probability of success as the metric, which was defined as a greater than 0 value for the lower bound of a 95% confidence interval of the difference in efficacy between SC-75416 and ibuprofen. Seven different design options were evaluated and the chosen design was a study with a 2:1 randomization with $N = 50$ patients per arm for the placebo and 60- and 180-mg SC-75416 oral solution treatments, and $N = 100$ patients per arm for the 360-mg SC-75416 oral solution and 400-mg ibuprofen treatments. A second post-oral surgery study was then conducted using a study design optimized to test the hypothesis that a dose of SC-75416 could achieve superior PR to 400-mg ibuprofen.

The results were remarkable, in that the observed results were consistent with model predictions and the data confirmed the hypothesis that a high dose (360 mg) of SC-75416 administered as an oral solution can achieve clinically relevant and statistically significant improvements in PR relative to 400-mg ibuprofen (Table 16.2).

16.3 Summary

The case studies presented herein highlight tangible impact (in terms of time, cost, and/or risk mitigation) achieved via the application of pharmacometric approaches to a variety of decisions that are at the core of clinical drug development. A summary of the impact of these approaches to drug development decision making is provided below:

- Case study 1: In the absence of head-to-head data, model-based meta-analysis was used to provide a quantitative basis for driving the decision to terminate the development of a compound with efficacy, but insufficient to be superior to SOC therapy. The framework is broadly applicable to support internal and external decision making at all stages of development.
- Case study 2: Use of model-based methods to design and analyze dose-finding studies resulted in efficiency gains by way of needing 437 fewer patients (~US$ 3 million in cost) compared to traditional methods. Prospective planning and pre-specification of the desired level of confidence in the magnitude of efficacy and safety resulted in larger than traditional phase 2 sample sizes, but ultimately allowed the identification of doses that produced the desired outcomes in phase 3 studies. Thus, model-based drug development should be viewed more as a risk mitigation tool than a cost-reduction tool.
- Case study 3: Use of model-based methods to bridge data across formulations and populations, along with the collection of extensive PK and PD data in the pediatric population including evaluation of the efficacy of two doses, resulted in the approval of interpolated doses and dosage forms that were not studied in the efficacy trial.
- Case study 4: Modeling and simulation providing the rationale, i.e., generated a hypothesis, for pursuing the high-dose strategy and designing a study to test the efficacy differentiation hypothesis that might not have otherwise been considered. The M and S strategy allowed progress to be made in understanding PK/PD relationships without having to wait for an improved solid dosage form to be developed, a time saving of approximately 9 months. Models that allowed predictions of clinically meaningful and statistically familiar end points were critical to gaining support to further invest in a study to evaluate the full potential of the molecule.

It must be mentioned, however, that these examples do not fully reflect the length and breadth of basic/fundamental pharmacometric research and application already demonstrated in the areas of systems biology, systems pharmacology, newer statistical methods as well as other types of applications to improve decision making in drug discovery and development (Table 16.3). The presented examples can be seen as defining the core pharmacometric activities that need to become standardized and "industrialized" so that resources can be better spent on the next frontiers of model-based development, such as characterization of drug target properties, better translation of drug attributes from preclinical to clinical space, and pharmacoeconomics.

Table 16.3 Overview of pharmacometric endeavors in inflammatory diseases

Drug	End point/disease	Model	Application(s)	Reference
Canakinumab	ACR20/RA	Longitudinal model-based meta-analysis (MBMA) model	Decision to terminate development Decision to terminate clinical development of canakinumab for the treatment of rheumatoid arthritis	Demin et al. (2012)
Biologics disease modifying anti-rheumatic drugs (DMARDs)	ACR20/RA	MBMA model	Indirect comparison of efficacy due to limited number of head-to-head trials Differences in efficacy and differential impact of dose titration were evaluated	Mandema et al. (2011)
Inhaled corticosteroids	Cortisol suppression/asthma and other conditions	Simulation using IDR model	Excel-based algorithm based on a PK/PD model to quantify and predict cumulative cortisol suppression for a variety of corticosteroids	Krishnaswami et al. (2000)
Ciclesonide and fluticasone propionate	Cortisol suppression/asthma and other conditions	Population PK/PD, IDR model	Characterization and model-based comparison of PK/PD properties of two compounds	Xu et al. (2010)
Prednisolone	PK/many conditions	Semi-mechanistic PK/PD model	Combines PK models for free prednisone and prednisolone, linear release PD model for cortisol suppression, and competitive protein binding between cortisol and prednisolone to predict total prednisolone concentrations in plasma	Xu et al. (2007)
Budesonide	Total lymphocyte and subsets and cortisol levels/asthma	IDR model with circadian rhythm	To evaluate the effect on the lymphocyte subsets relative to the effect on total lymphocytes To characterize cortisol suppression as a more sensitive marker for the systemic effect of corticosteroids	Stark et al. (2006)

Table 16.3 (continued)

Drug	End point/disease	Model	Application(s)	Reference
Certolizumab	ACR20/RA	Markov mixed-effects model	Accounts for potential serial correlation in ACR response to allow for more realistic simulations of the time course of ACR20 response	Lacroix et al. (2009)
SC-75416	Pain relief/post-oral surgery pain	PK/PD and dropout (survival) models	Provided increased confidence to pursue high-dose strategy and to test the efficacy differentiation hypothesis in a clinical trial	Kowalski et al. (2008)
Inhaled PF-00610355	Forced expiratory volume in one second (FEV1)/chronic obstructive pulmonary disease (COPD)	Longitudinal dose–response models	To characterize the dose–response relationship between two inhaled long-acting beta agonists (PF-00610355 and salmeterol) and FEV1 in order to inform dosing recommendations for future clinical trials in patients with COPD	Nielsen et al. (2012)
Tofacitinib	Health assessment questionaire (HAQ)/RA	Longitudinal dose-response model	To implement transformations of continuous bounded outcomes data A transformation strategy with a likelihood component for censoring was developed to promote the simplicity of model structures and to improve the plausibility of assumptions on the random effects	Hutmacher et al. (2011)
Celecoxib	JRA-30 definition of improvement/JRA	Mixed-effects logistic regression model	To derive dosing recommendations for the use of celecoxib in patients with juvenile rheumatoid arthritis (JRA) using PK and exposure response data	Krishnaswami et al. (2012)
Tofacitinib	ACR20/RA	Indirect latent variable response model	First application of an unobservable latent variable model, through which indirect response models can be linked with drug exposure	Hutmacher et al. (2008)

Table 16.3 (continued)

Drug	End point/disease	Model	Application(s)	Reference
Golimumab	ACR20,50,70/RA	Indirect latent variable response model	To characterize dose response using latent variable longitudinal dose response model	Hu et al. (2013)
Ciclosporine	Acute rejection/transplant	Time to event model	Describe acute rejections in pediatric renal transplant recipients treated with Ciclosporin A Optimize dose tapering	Frobel et al. (2013)
AZD-9773	Serum TNF-α/RA	IDR model	To simulate dosing options for a phase 2b study	Yates et al. (2012)
Anakinra	CIA rat model/RA	PK/PD/Disease progression	To characterize the effects of anakinra in collagen-induced arthritic (CIA) rats and explore the role of interleukin-1β (IL-1β) in rheumatoid arthritis	Liu et al. (2011)
Tocilizumab	DAS-28/RA	IDR model	Tocilizumab 8 mg/kg is more effective than 4 mg/kg in reducing disease activity	Levi et al. (2012)
RA therapies	ACR20/RA	Physiolab model platform	Deterministic simulation model to characterize life cycle of inflammatory cells, endothelium, synovial fibroblasts and chondrocytes and identify critical pathways (e.g., IL-12 and IL-15) to drive predicted disease outcome	Struemper et al. (2008)
Bone resorptive therapies	Multiple inputs, including active osteoblasts and active osteoclasts/osteoporosis and other skeletal diseases	Bone–cell interaction model/ Bone remodeling model/ RANK RANKL-OPG pathway model	To determine and evaluate potential therapies based on their efficacy using a small systems model that describes bone formation and resorption, providing insight that future models could be based on	Lemaire et al. (2004)

Table 16.3 (continued)

Drug	End point/disease	Model	Application(s)	Reference
Denosumab	NTX (a bone resorption biomarker) levels/multiple myeloma	PK/PD model using cellular bone homeostasis	To apply a cellular bone homeostasis model (a modification of the Lemaire model) to characterize the PD of denosumab in MM patients	Marathe et al. (2008)
Denosumab/Ibandronate	Levels NTX/CTX (bone resorption biomarkers) and lumbar BMD/osteoporosis	PK/PD model using cellular bone homeostasis	To characterize the PD properties of denosumab, and of ibandronate, using an integrated bone homeostasismodel in postmenopausal women To characterize the effects of these drugs on Lumbar BMD using a bone turnover model, thus providing clinical relevance	Marathe et al. (2011)
Denosumab	Multiple inputs, including active osteoblasts and active osteoclasts/various physiological and pathophysiological conditions re-bone remodeling such as osteoporosis	Reduced version of the Lemaire RANK RANKL-OPG pathway model	The conceptual bone cell interaction model by Lemaire could be reduced from a three- to a two-dimensional system. Reducing the model's complexity allowed for a transparent discussion of its dynamics and also opened the way for a geometric, two-dimensional analysis To show that on a time scale of disease progression and therapeutic intervention, the original Lemaire models and the simpler "reduced" models were found suitable for characterization of the end points tested with negligible differences in their dynamic properties	Schmidt et al. (2011)

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