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Pharmacokinetic/Pharmacodynamic Modeling in Inflammation

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Abstract

Inflammation is an array of immune responses to infection and injury. It results from a complex immune cascade and is the basis of many chronic diseases such as arthritis, diabetes, and cancer. Numerous mathematical models have been developed to describe the disease progression and effects of anti-inflammatory drugs. This review illustrates the state of the art in modeling the effects of diverse drugs for treating inflammation, describes relevant biomarkers amenable to modeling, and summarizes major advantages and limitations of the published pharmacokinetic/pharmacodynamic (PK/PD) models. Simple direct inhibitory models are often used to describe *in vitro* effects of anti-inflammatory drugs. Indirect response models are more mechanism based and have been widely applied to the turnover of symptoms and biomarkers. These, along with target-mediated and transduction models, have been successfully applied to capture the PK/PD of many anti-inflammatory drugs and describe disease progression of inflammation. Biologics have offered opportunities to address specific mechanisms of action, and evolve small systems models to quantitatively capture the underlying physiological processes. More advanced mechanistic models should allow evaluation of the roles of some key mediators in disease progression, assess drug interactions, and better translate drug properties from *in vitro* and animal data to patients.

Keywords

inflammation; pharmacokinetics; pharmacodynamics; arthritis; modeling

I. INTRODUCTION

The classic symptoms of inflammation include *rubor* (redness), *tumor* (swelling), *calor* (heat), *dolor* (pain), and *functio laesa* (loss of function).[1] An inflammatory response is beneficial since it plays an important physiological role in defense from invasion of pathogens and heralding wounds or other damage. When this protective mechanism becomes uncontrolled, it can lead to lethal outcomes, such as septic shock.[2]

Modeling and simulation are important for quantitation of experimental data and prediction and interpretation under new circumstances. Such approaches can help in evaluating the effectiveness of new therapeutic agents, understanding disease pathology, and facilitating the drug development process. Mechanism-based models allow assessing drug interventions on relevant biomarkers and the pathological network.[3] In this review, we summarize the basis, rationale, and array of PK/PD models that describe the inflammation mechanism and processes, and the effects of anti-inflammatory agents.

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II. THE INFLAMMATORY PATHWAY

A. Acute Inflammation

Much is understood about the invading agents and the subsequent inflammatory cascade. An acute inflammatory response follows four major processes, namely, invasion of infectious stimuli (often referred as inflammatory inducers), recognition of the agents by sensors, activation of inflammatory mediators, and modulation of target tissues by the mediators (Fig. 1).[4] Inflammation is triggered by infection or tissue injury, where the inducers can be exogenous (e.g., pathogens, such as bacteria, virus, allergens, irritants, toxic compounds, or commensal bacteria), or endogenously produced by damaged or malfunctioning tissues.[2] Examples of endogenous inducers include crystals of monosodium urate and calcium pyrophosphate dihydrate, and advanced glycation end products (AGEs). Inflammatory inducers are recognized by specific receptors (sensors) of the immune system, which are primarily toll-like receptors (TLRs) localized on immune cells such as mast cells and macrophages. [4] There are 10 TLRs expressed in humans, and each binds to specific ligands and has different cell localization.[1] Another inflammatory sensor is the nucleotide-binding oligomerization-domain protein (NOD)–like receptor (NLR).[2] These sensors are responsible for signaling the production and migration of inflammatory mediators.

On detection of invading agents by the sensors, immune cells produce inflammatory mediators. Most of these are produced by specialized leukocytes, such as tissue-resident macrophages and mast cells, or cells in local tissues.[2] Some preformed ones, such as histamine and serotonin, may be secreted from the granules of mast cells, basophils, or platelets, or converted from their precursors. [2] Inflammatory mediators can be categorized into seven groups: vasoactive amines, vasoactive peptides, fragments of complement components, lipid mediators, cytokines, chemokines, and proteolytic enzymes.[2] Although these mediators have characteristic roles in inflammation contributing to a specific response, some functions are overlapping (Table 1).

Inflammatory mediators elicit their effects in target cells and tissues. Some effects are ubiquitous [such as production of tumor necrosis factor (TNF)-α, and interleukin (IL)-1], whereas others only affect specific tissues.[2] The functional states of the target tissues are often the endpoints of interest where the severity of disease and PD effects can be measured. Therefore, they vary with the type of inflammatory condition being assessed.

B. Chronic Inflammation

Typically, the ultimate purpose of an inflammatory response is to remove the inciting stimuli, repair the affected sites, and allow return to homeostasis. If the elimination of invading inducers is not complete (as in transplantation), progression to chronic inflammation occurs, where the pathological mechanisms are more complicated and the outcomes are often more long lasting and detrimental. [1] Unlike acute inflammation, it is difficult to assign a “general pathway” due to the diversity of conditions. Many diseases, such as obesity, type 2 diabetes, neurodegenerative diseases, and cancer, have underlying chronic inflammation.[2,4,5]

III. ANTI-INFLAMMATORY AGENTS

There are numerous effective therapeutic agents available for treating inflammation. There are seven pathways where drugs and biologics may intervene. [1] The first is suppression of gene expression. This is the major mechanism of action of corticosteroids (CS), which are potent agents that mimic functions of cortisol and can inhibit transcription factors [for instance, nuclear factor (NF)-κB] that are inducers for many proinflammatory mediators.[6] The CS such as prednisolone are frequent choices for combination therapy owing to long

clinical experience. The second category is antiproliferative agents, such as methotrexate and leflunomide, which can hinder DNA synthesis by either blocking activity of essential enzymes or directly interrupting DNA replication. The third class of agents reduces expansion of immune cells. Cyclosporine, tacrolimus, and sirolimus inactivate the intracellular signaling of T cells, which, in turn, decreases production of proinflammatory mediators such as IL-2 and interferon (IFN)-γ.[6] They are often used to treat immune issues in transplantation.

Most drugs in the next four immunosuppressive pathways are biologics such as antibodies and fusion proteins. There are more than 25 antibodies approved for therapy, 30 in phase 3 clinical trials, and more than 250 in phase 1 and 2 studies as of January 2011.[7,8] Although structurally similar, different antibodies pose various mechanisms of action. Some of these are neutralization of specific cytokines (the fourth pathway), elimination of specific immune cells (the fifth), blockade of costimulation for T-cell activation (the sixth), and inhibition of cell adhesion (the seventh).[1]

Examples of approved anticytokine therapeutics include etanercept, infliximab, adalimumab (TNFα inhibitors), anakinra (IL-1 inhibitor), and tocilizumab (IL-6 receptor antagonist).[8] They are engineered to specifically bind to their soluble targets, which are crucial mediators in immune signaling and have strong proinflammatory activity. One concern is that unpredictable adverse effects may sometimes occur due to the pleiotropic nature of cytokines.[1] Other antibodies, such as rituximab and ofatumumab (anti-CD20), alemtuzumab (anti- CD52), and alefacept (anti-CD2), target reactive immune cells. They bind to the cell-surface receptors on antigen-bearing T or B cells, modulate their functions, then deplete them through antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC).[1,8]

One class of antibodies interrupts the costimulatory signals essential for complete T-cell activation. These include abatacept and belatacept.[9] They contain a domain of cytotoxic T-lymphocyte antigen (CTLA)-4, which competitively inhibits the binding between CD28 (on T cells) and CD80 / CD86 (on antigen-presenting cells).[10] These are used in transplantation and autoimmune diseases such as rheumatoid arthritis (RA).[1] The last general pathway is the prevention of migration and recruitment of immune cells to the target tissues. Efalizumab and natalizumab, as examples, block the accumulation of inflammatory cells by disrupting the interactions between the cell surface integrins and cell adhesion molecules.[1,8]

The NSAIDs, such as aspirin and ibuprofen, are inhibitors of cyclooxygenase (COX) and are effective in blocking the effects of eicosanoids (e.g., prostaglandins and thromboxanes), which regulate vasodilation and pain.[1] Although they have strong anti-inflammatory, antipyretic, and analgesic effects, their gastrointestinal or cardiovascular side effects are problematic.[6] Histamine is an autocoid and is important in IgE-mediated hypersensitivity (allergic) reactions. It is a local mediator that can cause contraction of smooth muscle and epithelial cells, leading to edema and pain. Antihistamines, such as loratadine and rantidine, target different histamine receptors (H1 and H2) and suppress clinical symptoms.[1] Tyrosine kinases, such as Janus kinases (JAKs) and Bruton's tyrosine kinases (BTKs), are important in many proliferative diseases such as leukemia, which also involves cytokine production.[11] Blockers of tyrosine kinase have anti-inflammatory effects.[6] There are other anti-inflammatory agents (such as protease inhibitors, statins, and inhibitors of complement activation) for which PK/PD modeling has not been performed.

IV. BIOMARKERS OF INFLAMMATION

Biomarkers provide signals about pathology of diseases and pharmacology of drugs that can herald therapeutic or toxic effects.[12,13] An ideal biomarker should have "consistent

characteristics with an acceptable sensitivity and specificity representing a specific toxicity or therapeutic effect of the drug, a specific physiological response to a treatment, a pathological progression or a physiological factor." [13] Numerous biomarkers have been utilized for quantifying anti-inflammatory drug responses at levels of cells, mediators, and target tissues.

A. Quantification of Immune Cell Responses

The activation of T cells serves in transmitting immune signals and generating immune mediators. Flow cytometry facilitates counting both total and selective immune cells with specific receptor expressions in blood. Immune cell responses can be assessed using mitogen-induced lymphocyte proliferation assays. Such assays are usually performed with splenocytes, isolated lymphocytes, or whole blood (WBLP), and can be conducted *in vitro* or *ex vivo*.[14–16] WBLP is preferable because it requires small blood volumes, reflects the natural milieu, and is simple for studying drug-drug interactions (DDI).[14–18] *Ex vivo* assays involve drug being dosed in study subjects before blood collection where one can assess the joint effects of drugs and metabolites.[15,19]

Methodology for direct lymphocyte counting is straightforward: after drug is given to study subjects, blood is collected at various time points, and the lymphocytes of interest (for example, those with a specific receptor expression, such as $CD4^+$) are quantified by flow cytometry. Such measurements are primarily for assessing cell-trafficking dynamics.[15,20–23]

B. Quantification of Immune Mediators

Choice of the mediators being measured depends on the pharmacology of the drug of interest. For example, concentrations of prostaglandin E_2 (PGE_2) and thromboxane B_2 (TXB_2) are often quantified as indicators for COX-2 and COX-1 activities.[24,25] Proinflammatory cytokines, such as TNFα and IL-1β, are widely used biomarkers for many therapeutic agents.[26–32] Measurement of target cytokine concentrations of anticytokine therapeutics allows direct assessment of their PK/PD.[33] The immune mediators are usually measured by two methods. The first is use of immunoassays, such as enzymelinked immunosorbent assays (ELISAs)[28–31,33–35] and radioimmunoassay (RIA),[36] and the other is *ex vivo* measurement of enzyme activity.[24,25,37] When measurement of protein concentrations of the mediators is not feasible (usually due to assay insensitivity), mRNA concentrations may be obtained by polymerase chain reaction (PCR) and used as a surrogate.[26,27]

C. Quantification of Immune Responses on Target Tissues

Inflammation is systemic. The endpoints of interest depend on the inflammatory condition producing five main symptoms. Although numerous approaches have been developed solely to measure the severity of symptoms, some have diagnostic value. For many immune-related diseases, such as RA and systemic lupus erythematosus (SLE), the American College of Rheumatology (ACR) has established sets of criteria and scores.[38]

1. Redness—Redness (erythema) is often a result of vasodilation and can be a form of hypersensitivity reaction or reflect a chronic inflammatory skin condition such as psoriasis.[22] This is also the basis of intradermal allergy testing.[39] During treatment of psoriasis, the psoriasis area and severity index (PASI) score, which includes redness, is recorded to monitor disease severity.[40] Malar rash (redness on cheek) is also one of the ACR criteria for SLE.[38] PK/PD models of PASI score and area of redness (wheal) have been published.[22,41,42]

2. Swelling—Swelling (edema) is caused by hyperplasia and local infiltration of immune cells, and is one of the main features of RA. In animal models, edema is determined by paw volumes using a digital caliper or a plethysmometer.[43] One classification criterion of RA is number of swollen or tender joints (joint involvement).[44] Clinical improvement of RA after drug therapy is commonly reported using ACR criteria such as ACR20, which reflects a 20% reduction of RA severity compared with the predose condition.[45] Edema is one of the most important disease endpoints for arthritis and inflammation and is included in PK/PD modeling reports of many anti-inflammatory agents.[24,27,37,46–51] Besides direct determination of paw edema, the lameness score and/or motility of the animal legs are used to assess functional impairment due to edema.[47,52,53]

3. Fever and Pain—Fever and pain are two disease endpoints often assessed when investigating efficacy of NSAIDs. These are COX inhibitors that block the effects of prostaglandins in triggering an increase in body temperature via the hypothalamus.[25] Body temperature is usually monitored by implanting a temperature transmitter[25] or using a thermometer.[52–55] Prostaglandins also potentiate pain responses,[1] NSAIDs are thus also effective as analgesics. Pain is often assessed by visual analogue scales (VAS) or the faces rating scale (FRS) in humans. These methods involve asking study subjects to profess how much pain they experience on a rating scale (e.g., from “no pain” to “pain as bad as it could be”).[56] In animals, pain measurement approaches include a hind paw thermal escape model using an analgesia meter[24,47,57] and a newer method referred to as “cat walk” analysis.[25,58] Pain is subjective and thus exhibits higher interindividual variability than other endpoints. Other approaches, such as pain-induced functional impairment, provide more objective testing.[59]

4. Other Endpoints—Intragastric pH is measured to assess drug effects on reducing secretion of gastric acid.[60–62] Agents such as H2 blockers are used for treatment of peptic ulcer, a chronic inflammation in the stomach usually caused by *Helicobacter Pylori*.[1] Other PD endpoints include assessing bone mineral density (BMD) for RA.[26,27]

V. PK/PD MODELING IN INFLAMMATION

A general paradigm that provides a conceptual basis for simple PK/PD models in inflammation is shown in Fig. 2. The drug PK is always of importance in controlling the time course of exposure and frequently biophase distribution or target site exposure needs consideration. Provocations of inflammation, either natural or experimental, result in an increase of diverse mediators, biomarkers, or cells that lead to tissue damage. The mechanisms of action of anti-inflammatory drugs are typically either reduction of formation of the mediators or cells (most agents) or binding and accelerated removal of such entities (some biologics). An array of simple to complex indirect response, transduction, and target-binding models allow quantitation of most anti-inflammatory drug responses.[63]

A. Modeling Drug Effects on Immune Cell Responses

We published a series of models to describe how CS interact with other agents or mediators using lymphocyte proliferation (WBLP) assays. The type of direct effect (E) equation commonly used for quantitating drug effects in cell cultures is

$$E = E_0 \left(1 - \frac{I_{\max} C}{IC_{50} + C}\right) \quad (1)$$

where E_0 is the baseline, $I_{\max}$ is the maximum fractional effect, and IC_{50} is the drug concentration (C) producing half-maximal inhibition. A power coefficient can be added.

There are numerous examples where this simple nonlinear inhibition equation describes the reduction of lymphocyte proliferation by various CS,[64,65] dehydroepiandrosterone,[16] tacrolimus, methylprednisolone,[66] recombinant IL-10,[17] cyclosporine, [34] sirolimus,[14] calcium channel blockers,[67] and aspirin.[68] The model used for fitting *ex vivo* WBLP data is more complex, since it accounts for temporal changes of both lymphocyte proliferation and cell numbers during drug exposure.[15,64] Figure 3 describes an experiment where prednisolone was dosed in normal subjects and inhibition of both lymphocyte trafficking and mitogen-stimulated WBLP were measured. The PK/PD model employed was able to capture both the *in vitro* and *ex vivo* actions of prednisolone.[14]

Determination of lymphocyte counts allows *in vivo* measurement of the time course of cells in blood. This type of "cell trafficking" data is usually characterized by indirect response models (IDRs), sometimes IDRs with a precursor compartment, or by target-mediated drug disposition (TMDD) models. The most common basic IDR model employed for anti-inflammatory drug effects is

$$\frac{dR}{dt}=k_{\text{in}}\left(1-\frac{I_{\max}C}{IC_{50}+C}\right)-k_{\text{out}}R \quad (2)$$

$$R(0)=R_0$$

where R is response, k_{in} is a zero-order production rate, k_{out} is a first-order removal rate constant, R_0 is baseline, and $I_{\max}$, C, and IC_{50} have the same meanings as in Eq. (1). Chakraborty et al. used such a simple IDR to describe the time courses of monocytes, lymphocytes, and neutrophils after joint dosing of prednisolone and recombinant IL-10 in humans.[19] Wu et al. also applied this IDR for the reduction of CD11a receptor expression after efalizumab in man.[69] Fisher et al. first applied Eq. (2) to describe movement of lymphocytes between blood and extravascular sites and effects of methylprednisolone.[70] This model became the basis for assessing lymphocyte trafficking after which many more advanced models were developed such as incorporating the circadian rhythms of endogenous CS as well as the effects of various exogenous CS.[15,20,21,23,64,65,71,72] Hong et al. modeled the interactions between cortisol and exogenous CS for lymphocyte trafficking.[64] Antibody alterations of lymphocyte counts required a TMDD model for efalizumab and TRX1 (a nondepleting anti-CD4 antibody).[22,73,74] TMDD models can simultaneously describe the time courses of drug (D), free receptors (R), and drug-receptor complexes (DR), and provide estimates of the drug-receptor binding and other PD parameters.[75] Ng et al. applied a TMDD model to describe the PK/PD of TRX1 and further utilized model simulations to make dosage suggestions for clinical studies.[73]

B. Modeling Drug Effects on Immune Mediators

For most studies where *ex vivo* stimulation of immune mediators was performed, Eq. (1) was applied to cell culture data.[25,29,32,34,37] Either the percentage inhibition ($100\cdot E/E_0$) or actual activity can be directly fitted to obtain $I_{\max}$ and IC_{50}. Qian et al. applied such a model for describing inhibition of TNFα production by DPC-333 in humans.[29]

Extended versions of IDRs with modified inputs (changes in *k*in) have been applied in modeling provocation time courses of immune mediators. [19,28,30,31,35,36] Gozzi et al. published a PK/PD model to describe the lag time observed for increase in TNFα after LPS induction and effect of susalimod.[30] This model is essentially a precursor IDR.[76] It was modified by Chakraborty et al.[28] and Wyska[31] for fitting time courses of TNFα and other mediators after LPS induction along with drug inhibition.

More advanced models have been developed for fitting more comprehensive immune mediator data to help resolve mechanisms of action. Vug-mesyster et al. used a TMDD model to account for the interaction between IL-13 and anti–IL-13 antibody. [33] The model described the natural turnover of IL-13 and considered both single and double binding of IL-13 to the antibody. The model developed by Earp et al. for the effects of dexamethasone on RA disease progression using a collagen-induced arthritic (CIA) rat model[27] employed a series of transduction compartments to capture the time courses of induction of TNFα, IL-6, and IL-1β mRNA (to be discussed later).

C. Modeling Drug Effects on Immune Responses on Target Tissues

Models in this category become complicated because the magnitude of the disease endpoints is controlled by more factors. In fact, biomarkers such as immune cells and mediators are the predecessors and contributors to the response factors in this group. Nevertheless, simple inhibitory models are still occasionally used for basic PD profiles. [41,61,62] Ikawa et al. adapted Eq. (1) to compare the changes in intragastric pH after doses of lafutidine and famotidine, with addition of a biophase compartment to capture the short time delays in the response.[62] An IDR model would have been more appropriate. The IDRs are widely used for describing turnover components of different disease endpoints. Simple IDR models have been applied to fit antipyretic effects of COX inhibitors.[47,52,55,77]

Figure 4 shows an excellent example of using a simple IDR for fitting antinociceptive effects of tolmetin in rats.[59] The investigators gave a wide range of drug doses, and were able to capture all PK/PD profiles jointly using a population-fitting approach to generate the pharmacologic capacity (I_{max}) and sensitivity (IC_{50}) parameters causing inhibition of the inflammatory process. The IDR models reflective of inhibition of $k$in and their extensions are most commonplace in modeling anti-inflammatory effects because of the paradigm that drugs usually inhibit the provocation mechanism (Fig. 2)

Advantages of using IDR models for modeling are that they are very flexible, allow easy modifications, and basically mimic the pathophysiology of many disease conditions. Some IDR models incorporate a placebo effect. This was done to describe the ACR score for RA and the PASI score for psoriasis.[42, 48, 78] Hu et al. modeled the placebo effect with an empirical exponential function that was included in the inhibition function for the drug effect.[78] Lee et al. characterized etanercept effects in RA patients where the placebo effect was modeled with a polynomial function.[46]

Simple IDRs assume that the baseline of response is constant over time. Baseline responses often fluctuate over time due to physiology (e.g., circadian rhythms) and disease progression–related reasons. Added mathematical functions are needed to capture these changes. Some of these functions can be as simple as a linear function, as in studies where a first-order rate constant describes the natural production of gastric acid[60] and natural paw growth.[49] Josa et al. used a nonlinear time-dependent function $IR(t)$ in place of k_{in} to describe the increased activity of mediators causing fever after LPS stimulation in rats. Naproxen was assumed to inhibit the $IR(t)$ function.[54] There are similar models in the literature.[24, 53] Some models describe disease progression by applying an empirical function to replace k_{in} or k_{out}. Giraudel et al. used a gamma function to replace k_{in} in modeling kaolin-induced inflammation and effect of meloxicam in cats.[47] Vasquez-Bahena et al. also used a gamma function for capturing effects of lumiracoxib.[79] Other small modifications can be implemented to include disease progression in models. ([49, 80, 81]) An interesting model by Krekels et al. used a precursor IDR to characterize the effect of naproxen on reducing fever with a “modified Bateman function” for k_{in} to fit the time profiles of carrageenan-induced guarding index (a pain measurement) and yeast-induced fever in rats.[25]

D. Modeling Clinical Symptoms

Investigators in clinical pharmacology often encounter clinical data that are discrete measurements (scores) that are determined by physicians to indicate disease severity. Examples of this include the ACR20, ACR50, and ACR70 in RA, and PASI in psoriasis (see Section IV). Use of IDR models is common for modeling such data. Hu et al. published two articles applying Eq. (2) (with incorporation of placebo effect) to describe effects of golimumab on ACR scores in RA patients.[48, 51] Ng et al. also used a IDR-based model to describe the temporal changes of PASI score in psoriasis patients receiving efalizumab.[22] Other approaches, such as logistic regression,[82–84] have also been used.

E. Animal Scaling

Allometric scaling offers interspecies calculation methods for physiological processes and PK based on body sizes using rules of comparative anatomy, physiology, biochemistry, and cellular structure.[85–87] Lepist et al. digitized S(+)-ketoprofen PK/PD data (PGE_2 indicating COX-1 activity and TXB_2 indicating COX-2 activity) in sheep, horse, calf, and goat, and fitted these data with a two-compartment model for PK and IDR models for PD.[88] The PK data scaled well, but the PD data were variable and generally did not follow any common rules. Mukherjee et al. examined a wide array of NSAIDs and demonstrated how the ED_{50} from the carrageenan rat paw model correlates well with the typical human dose of such drugs.[89] Mager et al. reviewed related concepts and efforts to scale PD from animals to man.[90]

A mix of data sources can be useful for translational purposes. Betts et al. utilized rat and monkey *in vitro* and *in vivo* data in a complex TMDD model to predict human PK/PD profiles of PF-04840082.[91] This is a humanized anti-Dickkopf-1 (Dkk1) IgG antibody for the treatment of osteoporosis.

VI. MECHANISM-BASED MODELING IN INFLAMMATION

More complex mechanism-based disease progression models can give insights into the temporal changes of important pathological mediators or factors and how drugs may affect different processes of disease progression.[73]

A. Bone Homeostasis Models

Joint destruction is one of the major symptoms in RA. Bone composition is balanced by osteoblasts and osteoclasts through the critical receptor activator of NF-κB (RANK)-RANK ligand (RANKL)-osteoprotegerin (OPG) pathway.[92] In RA patients, inflammatory cytokines (TNFα, IL-1β, and IL-6) are overproduced and stimulate production of RANKL to disturb the balance causing activation of osteoclasts with subsequent bone destruction.[93]

Lemaire et al. proposed the first small systems model incorporating RANK-RANKL-OPG pathway and its specific regulatory factors, transforming growth factor β (TGF-β) and parathyroid hormone (PTH, the most important hormone regulating bone remodeling) to describe bone formation and resorption. [94] Marathe et al. successfully applied a modified model to the antibody denosumab, an inhibitor of RANKL.[95] They expanded the model to describe the effects of osteoclast-osteoblast interplay on BMD[96] (Fig. 5). The model captured the effects of a range of doses of denosumab both on the resorption biomarker, N-telopeptide of type I collagen (NTX), and on the ultimate endpoint, BMD. The addition of this clinical endpoint gave this model more power and clinical relevance. The Danhof group has addressed approaches to simplify the Lemaire model and yet provide sufficient model power to capture the physiological changes and drug effects under different meaningful scenarios.[97]

Other models of this kind include a physiologically based biological model proposed by Peterson and Riggs incorporating the previous cellular bone homeostasis model and calcium-phosphate concentrations to describe bone remodeling and calcium homeostasis.[98] Changes of bone volume, impact of cell maturation on RANKL and OPG expression, and differentiation of TGF-β impact on different bone cells were also considered in another extended cellular bone homeostasis model.[99]

B. Mechanism-Based Models of Inflammation

There are a limited number of small systems models of inflammation. Earp et al. developed a mechanism-based model of RA based on data obtained from CIA rats.[26, 27] Figure 6 displays the structure of the model. The scheme combines several simple model components. Part captures the PK of dexamethasone (as shown) and receptor-mediated dynamics of CS and the glucocorticoid receptor (GR). Several other elements are derivations of inhibitory IDRs with the addition of transduction compartments to mimic the long time delay of cytokine mRNA induction. The model successfully captured the time courses of inhibition of three proinflammatory cytokine mRNAs (only IL-1β is shown) and their joint provocation of paw edema as well as changes in paw BMD.

Liu et al. developed a simpler CIA rat PK/PD model,[37] but there was no cytokine (mediator) data. The model has transduction steps for the time delays affecting the rate constant k_{out}, and the reduction of ankle edema was related to the decrease in BTK enzyme activity caused by the investigational drug GDC-0834. The inhibition in BTK enzyme activity was calculated with an inhibitory function using *in vivo* data collected in another group of animals and then applied as a forcing function in the model fitting. More recently, a mechanism-based model was published to describe the effects of methylprednisolone on inducible nitric oxide synthase (iNOS) mRNA expression as well as the disposition kinetics of NO in a rat model of lipopolysaccharide (LPS)–induced inflammation. [100] This model combined the use of simple and precursor-pool IDR models for quantitating the turnover of iNOS mRNA expression in lung and production of NO in plasma. These types of mechanism-based models provide connections between different components for drug, mediators, and disease endpoints.

C. System Biology–Based Models of Inflammation

There are numerous mathematical models to describe inflammatory processes, pathological networks in immune diseases, and interactions between inflammatory mediators by systems modelers. [101–109] Such a modeling approach is considered “bottom up,” in which investigators subjectively harvest the best information from the literature in assembling the model. There is usually none or little experimental data collected for components in the complex mathematical schemes. These models are useful for simulations that address problems such as therapeutic interventions at different phases of inflammation[104] and why patients may respond differently toward the same drug treatment.[105] Often, these are questions that cannot be answered by experiments due to technical complexities or ethical difficulties. An interesting approach is called “agent-based modeling,” which sets up a list of rules that the elements in the model must follow based on the known facts of the immune network. Dong et al. used this method to describe time profiles of different immune cells and mediators following endotoxin-induced acute inflammation.[108]

VII. FUTURE EFFORTS AND PERSPECTIVES

Both the expansion of knowledge of inflammation and immune responses and the array of therapeutic agents with different mechanisms of action offer increasing opportunities for application of PK/PD/disease models. As noted by Earp et al.,[26] drug interventions allow

probing of biological systems to disturb the natural or pathological homeostasis permitting new insights into determinants of complex systems. While simple direct, IDR, transduction, and TMDD models have proven useful in quantitating diverse types of biomarkers, symptoms, and anti-inflammatory effects, the same models can serve as components of more complex small systems models. The PK/PD models offer promise of better mechanistic understanding of drug interactions that may ultimately be of clinical benefit. They can serve a translational role in melding relevant information from diverse *in vitro*, animal, and clinical sources. Inflammation models will need coupling with other disease models where inflammation is an underlying factor such as in diabetes, cancer, and neurodegenerative disease. Finally, as with all models, PK/PD models enable a shared understanding of physiologic and pharmacologic systems among those interested in advancing their fields in both a conceptual and quantitative manner.

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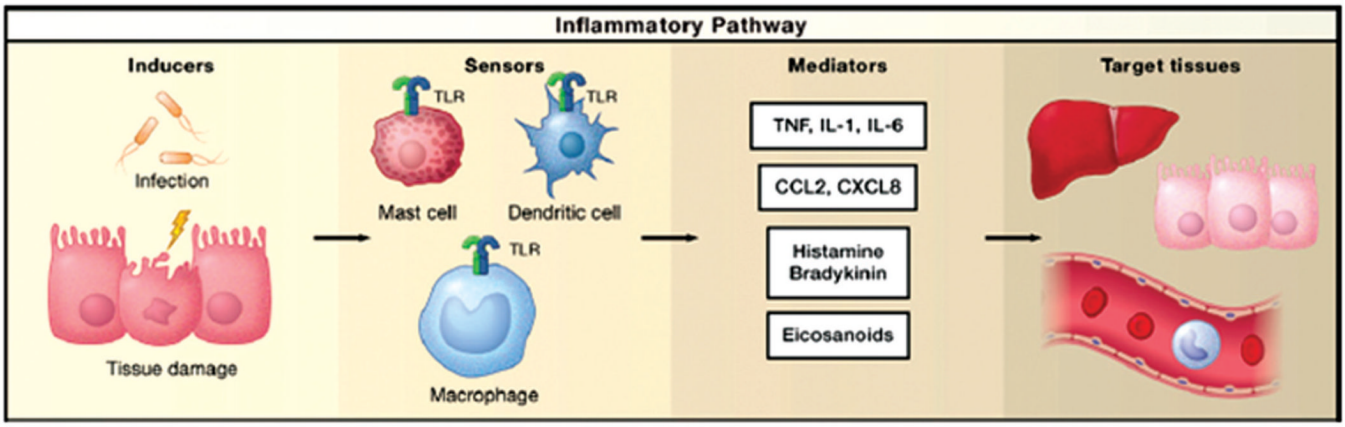

FIGURE 1.

The four main components in inflammatory pathway, adapted from Ref. 4. Inflammation is initiated by immune inducers, which are recognized by sensors (e.g., toll-like receptors) on immune cells, followed by the secretion of immune mediators (e.g., TNFα, IL-1β, and IL-6), and finally these mediators elicit their effects on target tissues.

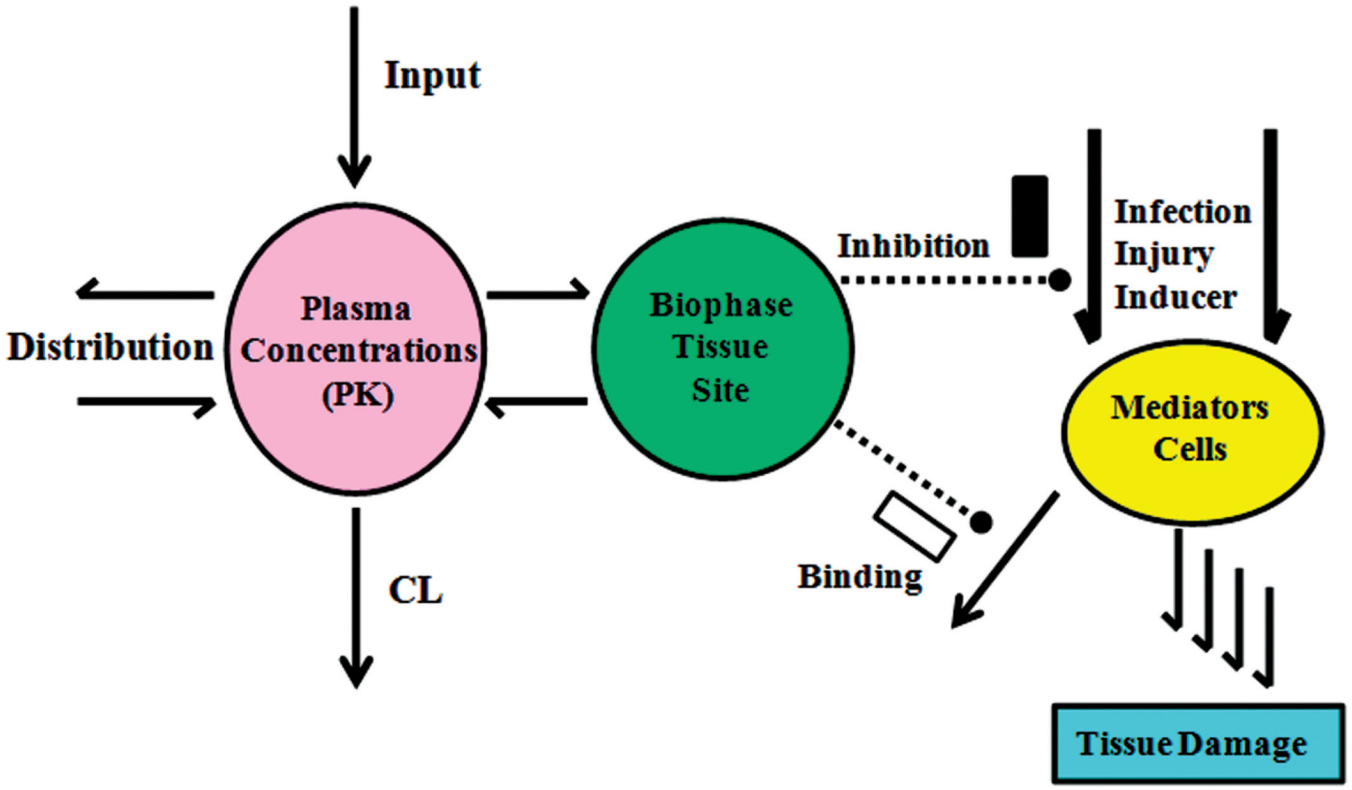

FIGURE 2.

General PK/PD paradigm that accounts for the primary factors governing the effects of most anti-inflammatory agents. The pharmacokinetics, target site drug distribution, mechanisms of drug action, inflammatory provocation processes, resultant mediators or biomarkers, and target tissues are primary components needing recognition in most models.

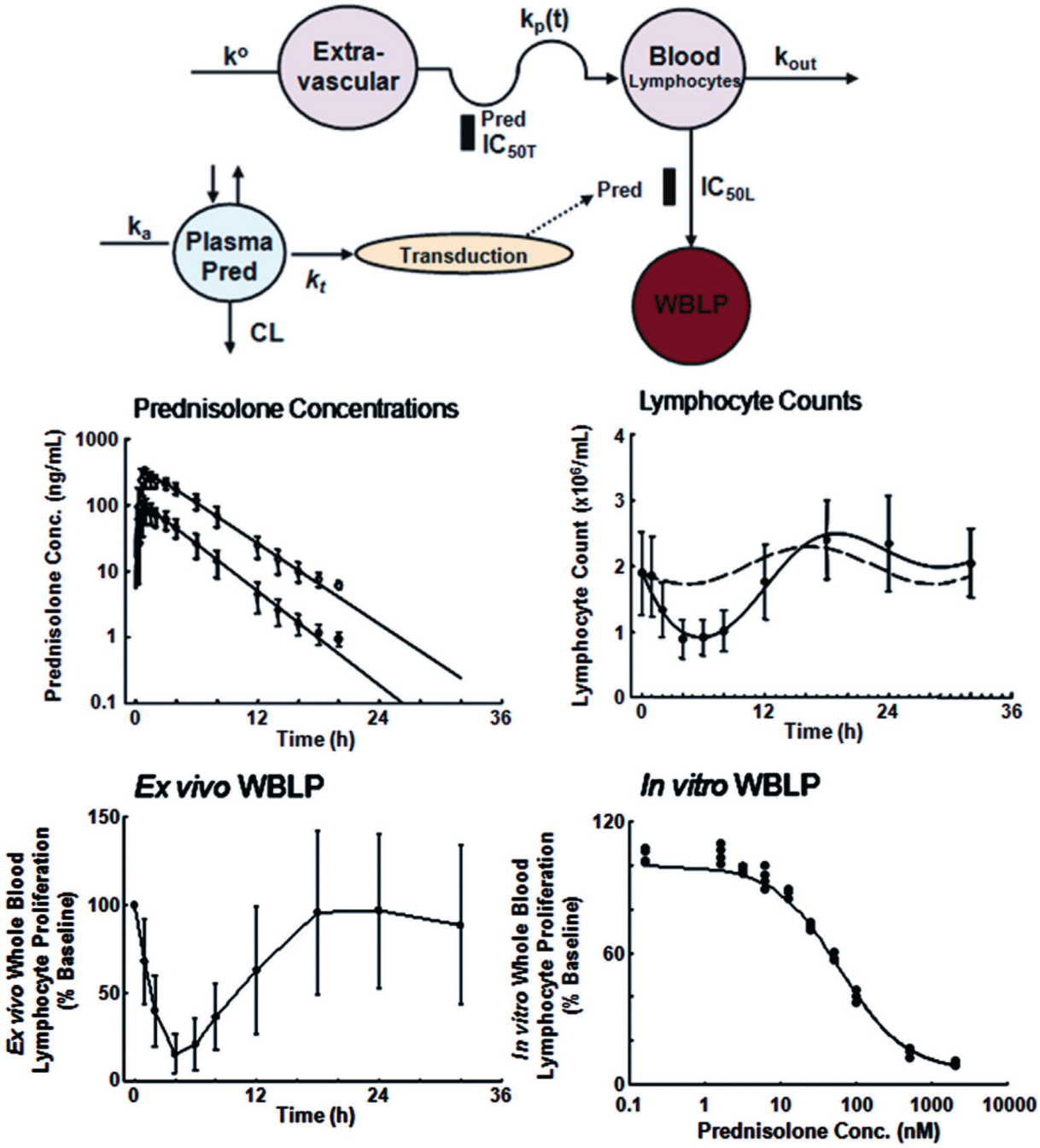

FIGURE 3.

PK/PD modeling of the effects of prednisolone on human lymphocytes, adapted from Ref. 15. Top panel shows the model schematic used for all data fitting. Middle panels are concentration-time profiles of total (open circles) and unbound (closed circles) prednisolone (mean ± SD), and time course of T-lymphocyte cell counts with circadian baseline (broken line) and after prednisolone (closed circles and solid line). Bottom panels depict time course of *ex vivo* WBLP expressed as percent of baseline (mean ± SD) and concentration-response curve of *in vitro* added prednisolone for inhibition of WBLP. Prednisolone acts on both lymphocyte trafficking and inhibition of mitogen-stimulated lymphocyte proliferation.

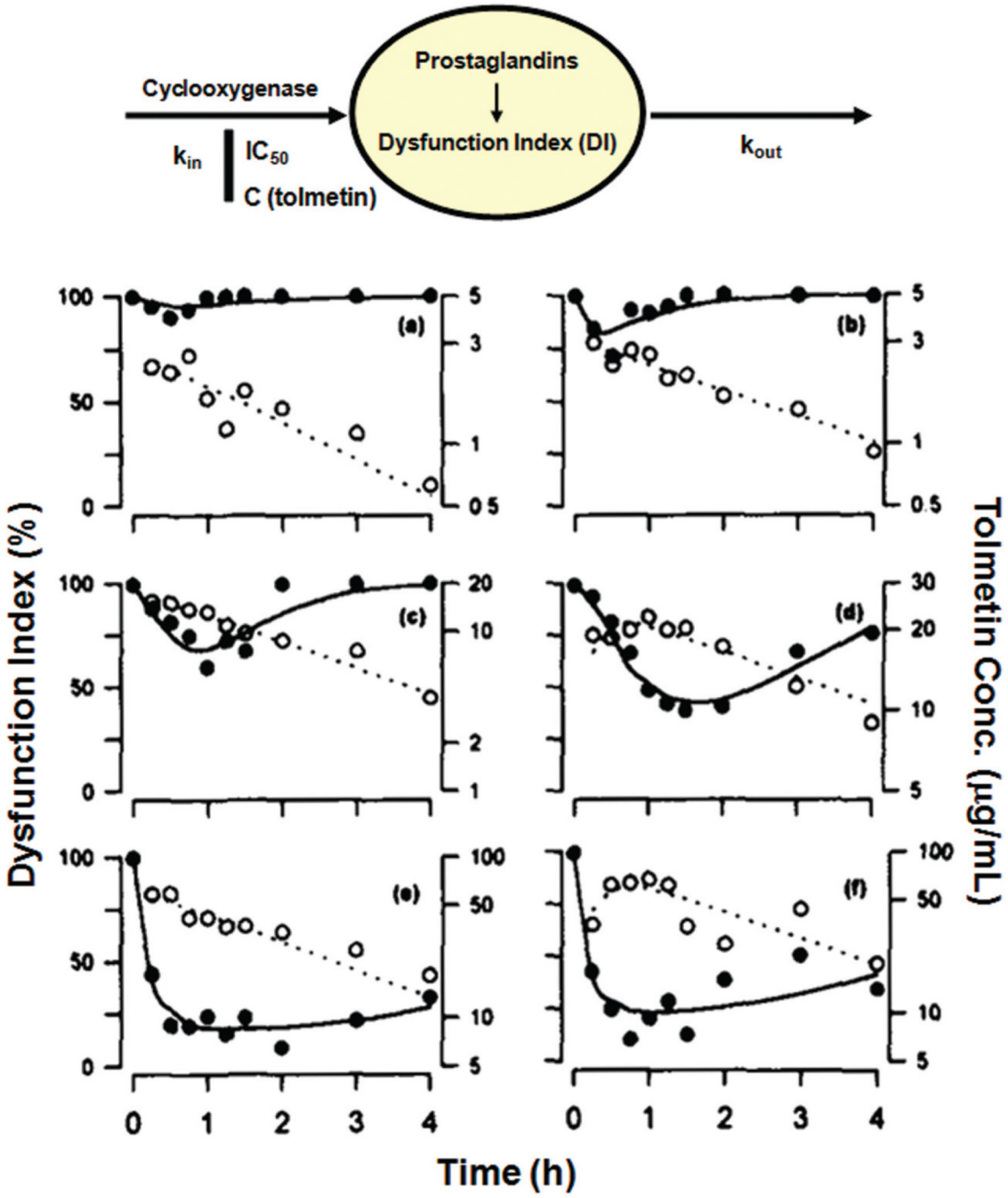

FIGURE 4.

PK/PD modeling of antinociceptive effects (dysfunction index) of tolmetin in rats, adapted from Ref. 59. Top panel shows the model schematic used for fitting of data. Lower panels show PK/PD time profiles of tolmetin in selected rats. Open circles are tolmetin blood concentrations and closed circles are dysfunction index values (%). The panels indicate doses of (a) 1, (b) 3.2, (c) 10, (d) 31.6, (e) 56.2, and (f) 100 mg/kg tolmetin given orally to the rats.

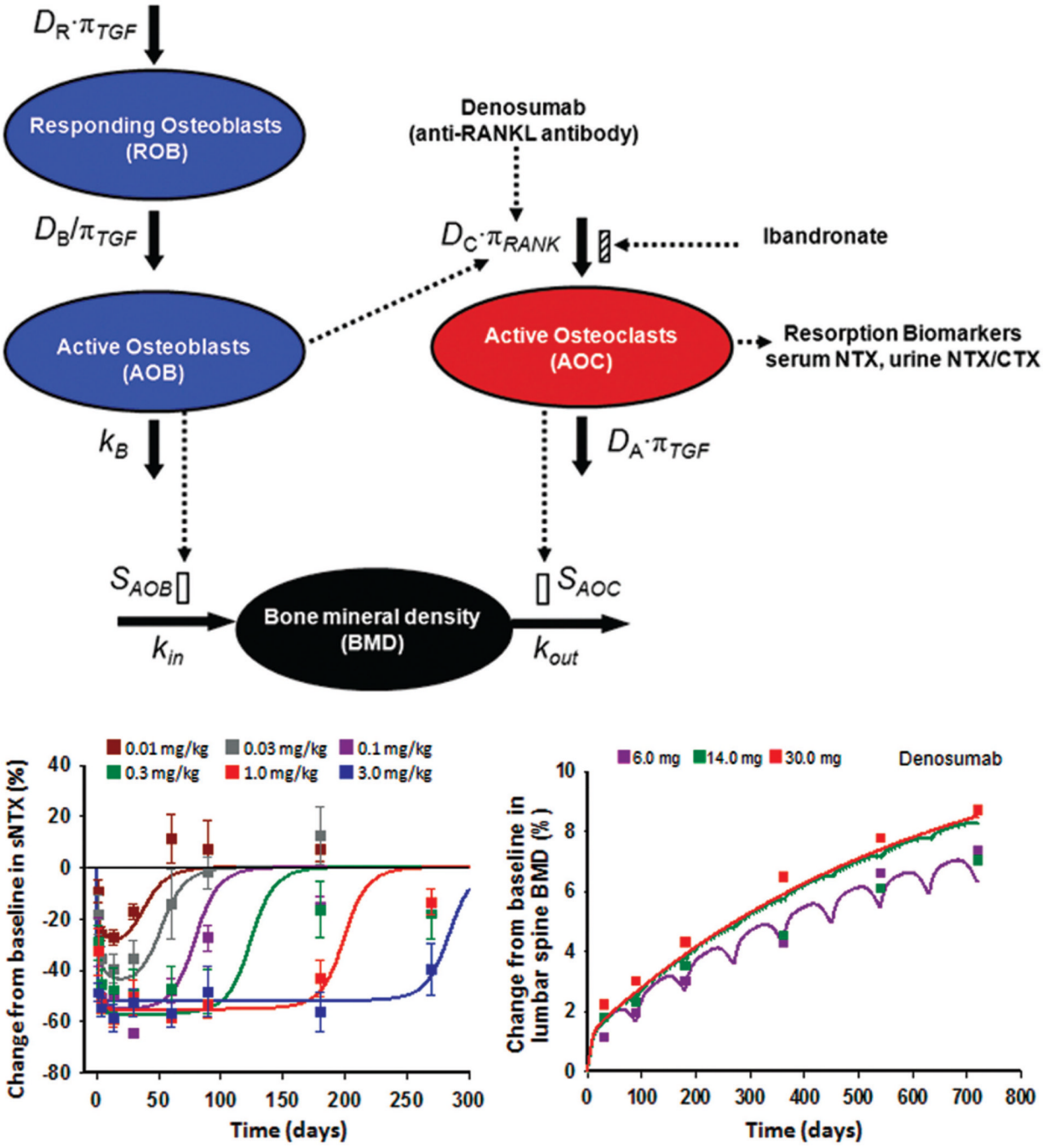

FIGURE 5.

Bone homeostasis model describing effects of denosumab and ibandronate in healthy women, adapted with permission from Ref. 96. Top panel shows model schematic used for fitting data. Left panel depicts time course of changes of serum N-telopeptide of type I collagen (NTX), a biomarker for active osteoclasts (AOC), after single subcutaneous (SC) doses of denosumab as listed. Data are mean ± SD and normalized with baseline NTX. Right panel shows time course of lumbar spine BMD after multiple SC doses of denosumab.

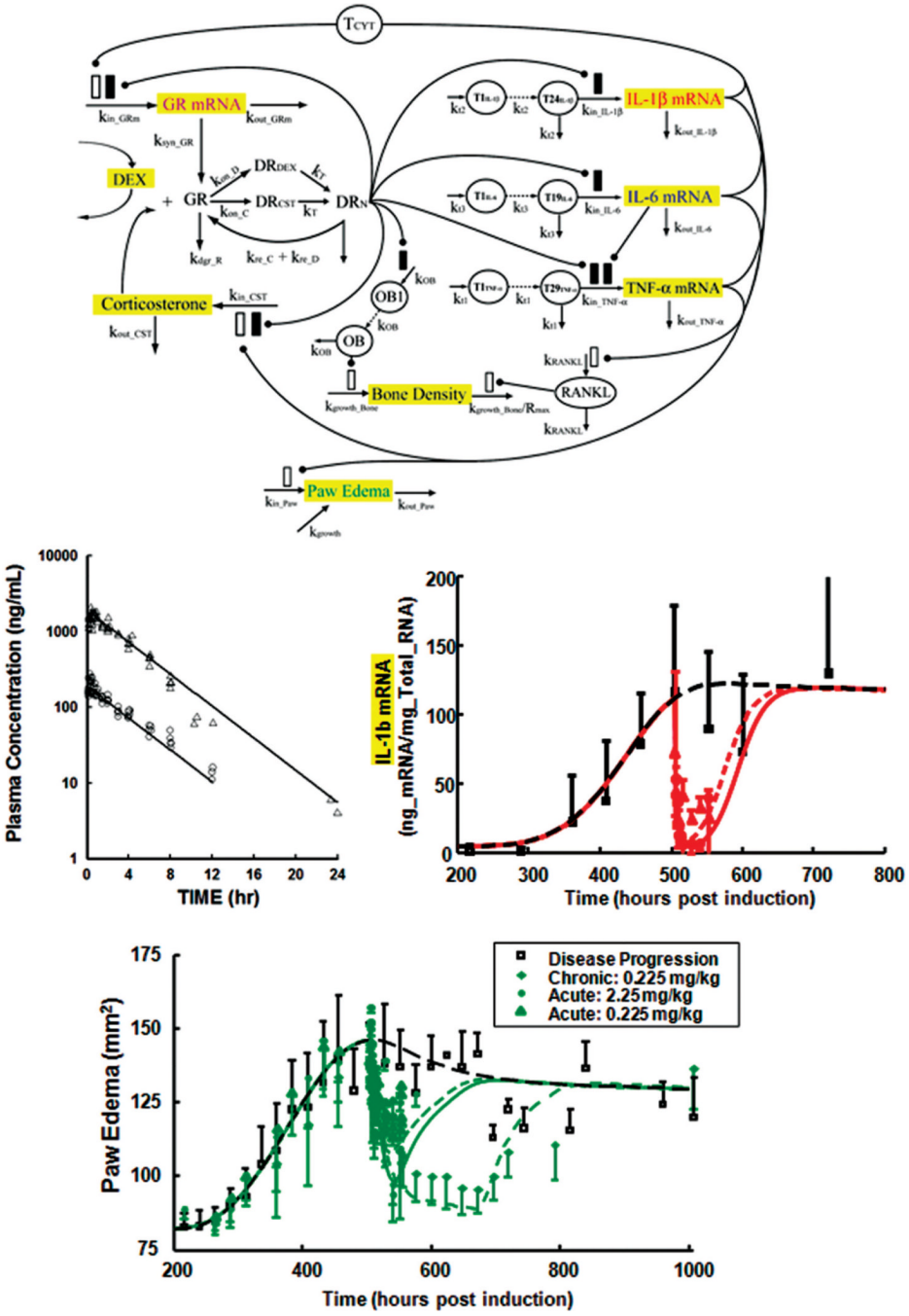

FIGURE 6.

PK/PD/disease modeling of the effects of dexamethasone in CIA rats, adapted from Ref. 27. Top panel shows model schematic used for fitting data. Center panels depict concentration-time profiles of dexamethasone at two dose levels, i.e., 2.25 mg/kg (open triangles) and 0.225 mg/kg (circles), and time course of paw IL-1β mRNA concentrations (mean ± SD) in rats after CIA induction and after single doses of dexamethasone. Bottom panel shows time course of paw edema (mean ± SD) in rats after CIA induction for untreated rats (open squares), and 2.25 mg/kg single-dose (closed circles), 0.225 mg/kg single-dose (open triangles), and 0.225 mg/kg multiple-dose (diamonds) dexamethasone groups.

TABLE 1

Inflammatory mediators and responses, adapted from Ref. 1

Vasodilation	**Increased vascular permeability**	**Chemotaxis and leukocyte activation**
Prostaglandins (PGI_2, PGE_1, PGE_2, PGD_2) Nitric oxide (NO)	Histamine Complement components (C3a, C5a) Bradykinin Leukotrienes (LTC_4, LTD_4, LTE_4), Platelet-activating factor Substance P Calcitonin gene-related peptide (CGRP)	C5a LTB_4 Lipoxins (LXA_4, LXB_4) Bacterial products
Tissue damage	**Fever**	**Pain**
Neutrophil Macrophage Lysosomal products Oxygen radicals NO	Interleukin-1 (IL-1) IL-6T Tumor necrosis factor (TNF) LTB_4 LXA_4 and LXB_4	PGE_2 and PGI_2 Bradykinin CGRP