Review Article

Biological Products for the Treatment of Psoriasis: Therapeutic Targets, Pharmacodynamics and Disease-Drug-Drug Interaction Implications

Jie Wang,¹ Yow-Ming C. Wang,^{1,2} and Hae-Young Ahn¹

Received 18 April 2014; accepted 11 June 2014; published online 4 July 2014

Abstract. Psoriasis is a chronic inflammatory skin disease condition that involves altered expression of a broad spectrum of proinflammatory cytokines which are associated with activation of T cells and proliferation of keratinocytes. Currently approved biological products for psoriasis treatment fall into two main classes: cytokine modulators and biologics targeting T cells. In psoriatic patients, elevated levels of proinflammatory cytokines are observed. Elevated proinflammatory cytokines can suppress some cytochrome P450 (CYP) enzymes, and the treatment of psoriasis with biological products can reduce proinflammatory cytokine levels. Therefore, the exposure of CYP substrate drugs is anticipated to be affected by the psoriasis disease resulting in a higher exposure than in healthy state (named disease-drug interaction) as well as by the biological treatments due to disease improvements resulting in a decrease in exposure (named disease-drug-drug interaction, disease-DDI). However, the quantitative impact on CYP substrate exposure due to disease or due to treatment with biological products remains to be evaluated. The objective of the current review is to provide an overview of the therapeutic targets and cytokine-related pharmacodynamic effects of biological products in psoriasis treatment with a particular focus on their implications for disease-DDI. The clinical study design considerations for psoriasis disease-DDI evaluation are also discussed.

KEY WORDS: disease-drug-drug interactions (Disease-DDI); inflammatory disease; IL-6; interleukin-6; proinflammatory cytokines; psoriasis.

INTRODUCTION

Psoriasis represents a chronic skin disease affecting approximately 2–3% population globally and is characterized by recurrent episodes of erythematous skin plaques with irregular borders and silvery scales (1–3). Conventional therapies for psoriasis have not been fully satisfactory (4). Biological products have been shown to be highly effective and represent important treatment options for psoriasis (5,6). Currently approved biological therapies are indicated for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidate for phototherapy or systemic

therapy. Approved dosing regimens of biologics for psoriasis treatment often include one for induction treatment and one for maintenance treatment because of the chronic nature of the disease. The induction dose regimen may contain higher starting doses and/or more frequent dosing to achieve the desired steady state concentrations quickly for a potential rapid onset of response. The purpose of maintenance treatment is to maintain response in responders and a lower and/or less frequent dosing regimen may be sufficient. Table I summarizes the pharmacokinetic (PK) properties and dosing regimens for the four anti-cytokine products (etanercept, infliximab, adalimumab, and ustekinumab) approved for psoriasis treatment. Psoriasis is increasingly a first-choice disease condition for proof-of-principle clinical trials in the development of new biological products for chronic inflammatory diseases, as is the case for ustekinumab.

With both environmental and genetic factors contributing to its pathogenesis, psoriasis is considered as a systemic inflammatory disease associated with activation of T cells, secretion of proinflammatory cytokines, and proliferation of keratinocytes (7,8). The inflammatory process of psoriasis involves altered expression of a broad spectrum of proinflammatory and anti-inflammatory cytokines, and elevated levels of proinflammatory cytokines are observed in psoriatic patients (9–15). Proinflammatory cytokines have been shown to modify the formation, stability, and activity of cytochrome P450 (CYP) enzymes and, therefore, have the potential to alter the systemic exposure of concomitantly administered

The opinions expressed in this article are those of the authors who are affiliated with the United States Food and Drug Administration (FDA) and do not necessarily reflect the official views or policies of the FDA. The authors did not receive external funding for this project.

¹ Division of Clinical Pharmacology III, Office of Clinical Pharmacology, Office of Translational Sciences, Center for Drug Evaluation and Research, US Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, Maryland 20993, USA.

² To whom correspondence should be addressed. (e-mail: yowming.wang@fda.hhs.gov)

ABBREVIATIONS: CYP, Cytochrome P450; Disease-DDI, Disease-drug-drug interactions; IL, Interleukin; TNF α , Tumor necrosis factor α .

Table I. Approved Dosing Regimens for the Four Anti-cytokine Biologics in Psoriasis Treatment. The Data were Obtained from Product Labeling and Reviews Through Drugs@FDA

	Etanercept	Infliximab	Adalimumab	Ustekinumab
Molecular Weight	~150 kDa	~149 kDa	~148 kDa	~148–150 kDa
Route of administration	SC injection	IV infusion	SC injection	SC injection
Half-life	102±30 h (mean±SD)	7.7–9.5 days (median)	2 weeks (mean)	3 weeks ^a (median)
Dosing regimen	50 mg twice weekly for 3 months, then 50 mg weekly	5 mg/kg at Weeks 0, 2, and 6, then every 8 weeks	80 mg initial dose, then 40 mg eow and from Week 1	45 or 90 mg at Weeks 0 and 4, then every 12 weeks ^b

^a The half-life values for ustekinumab are reported in the product labeling as 14.9±4.6 to 45.6±80.2 days (mean±SD) across different studies. In this review paper, the ustekinumab half-life value of 3 weeks is based on PK results from the approved 45 and 90 mg doses.

^b For patients weighing ≤100 kg (220 lbs), the recommended dose is 45 mg initially and 4 weeks later, followed by 45 mg every 12 weeks. For patients weighing >100 kg (220 lbs), the recommended dose is 90 mg initially and 4 weeks later, followed by 90 mg every 12 weeks. *eow* every other week; *kDa* kilodaltons; *SC* subcutaneous; *IV* intravenous

drugs that are substrates for CYP enzymes, leading to the occurrence of disease-drug interactions (16–18). In turn, the biological products for psoriasis treatment could modulate the proinflammatory cytokine levels and influence the expression of specific CYP enzymes as well as the exposure of CYP enzyme substrates, which is considered psoriasis disease-drug-drug interactions (disease-DDI). The consequence of the disease-DDI would be a loss of efficacy of the CYP substrate drugs.

In this review, we aim to (a) provide an overview of the therapeutic targets, the mechanisms of action, and the cytokine-related pharmacodynamic effects of biological products used for psoriasis treatment in Part 1, (b) discuss the implications for psoriasis disease-DDI in Part 2, (c) present study design considerations for psoriasis disease-DDI clinical evaluation in Part 3, and (d) provide our perspectives and conclusions in Part 4.

PART 1: THERAPEUTIC TARGETS AND PHARMACODYNAMICS

Based on the mechanisms of action, the biological products for psoriasis treatment can be categorized into two main classes: cytokine modulators (anti-cytokines) and biologics targeting T cells (Table II) (19–26). Four anti-cytokines have been approved in the USA for the treatment of psoriasis: infliximab, adalimumab, etanercept, and ustekinumab. The approved biologics targeting T cells include efalizumab and alefacept, however, both have been voluntarily withdrawn from the market in the USA (9,27). Focusing on these approved biological products with clinically validated therapeutic targets, we provide an overview of their mechanisms of action and the related pharmacodynamic characteristics. Readers are also referred to other publications for even broader discussions of the emerging new therapeutic targets and biomarkers in psoriasis research which may foster future personalized therapies for psoriasis treatment (28–33).

Anti-cytokines Targeting TNF α

Three of four approved anti-cytokines are targeting tumor necrosis factor α (TNF α): infliximab, adalimumab, and etanercept. Infliximab and adalimumab are monoclonal

antibodies with binding specificity to TNF α , whereas etanercept is a fusion protein and binds to both TNF α and TNF β . All three anti-cytokines block the interaction of TNF α with its receptors. Other notable TNF α inhibitors, e.g., certolizumab pegol and golimumab, have been approved for the treatment of rheumatoid arthritis (RA) and other inflammatory diseases, and they have ongoing clinical investigations in subjects with psoriasis (34–37).

Anti-TNF α treatment has been generally found to reduce the epidermal thickness and infiltration of inflammatory cells in histological studies. TNF α is a naturally occurring proinflammatory cytokine involved in immune responses (38), and elevated levels of TNF α were found in psoriasis plaques and serum (39,40). Serum TNF α level was shown to be correlated with disease severity and the effectiveness of treatment in a clinical trial with 30 psoriatic subjects (40). TNF α levels in lesional psoriatic skin were reported in a small study to be reduced in psoriatic subjects received adalimumab treatment (41). Additionally, anti-TNF α treatment was reported to affect other cytokine levels; for example, effective treatment of psoriasis with etanercept was associated with reduced serum levels of IL-17 and IL-22 (42), suggesting the interconnectivity of the cytokine network in inflammatory conditions.

Anti-cytokines Targeting IL-12/Th1 and IL-23/Th17

Ustekinumab is unique among the currently approved anti-cytokine biologics because psoriasis is its first approved indication. Ustekinumab targets the p40 protein subunit used by both interleukins (IL)-12 and IL-23, and inhibits both IL-12/Th1 and IL-23/Th17 pathways (43,44). Briakinumab, another IL-12/23p40 antagonist, was in development for psoriasis treatment, but its biological license application was withdrawn (5,45). Several emerging anti-cytokines are being developed for more selective inhibition of the IL-23/Th17 pathway (46), which include biologics with binding specificity to IL-23p19, e.g., CNTO 1959 and SCH 900222 (5,6,47), and biologics targeting IL-17 or IL-17 receptors, e.g., brodalumab, ixekizumab, and secukinumab (5,48–52).

IL-12 and IL-23 are naturally occurring proinflammatory cytokines involved in immune responses (53–55). Prior to the discovery of the IL-23/Th17 pathway, psoriasis was only

Table II. Overview of Biological Products for Psoriasis Treatment

Biologics Classes	Therapeutic Targets	Product name	Molecular structure	Development Status
Anti-cytokines	TNF α	etanercept	Fusion protein	^a Approved
		infliximab	Chimeric IgG1 κ mAb	^a Approved
		adalimumab	Human IgG1 mAb	^a Approved
		certolizumab pegol	Human Fab' fragment conjugated to 40 kDa PEG	^b Approved
	IL-12/23p40	golimumab	Human IgG1 κ mAb	^b Approved
		ustekinumab	Human IgG1 κ mAb	^a Approved
		briakinumab	Human IgG1 mAb	In clinical trials
	IL-23p19	guselkumab	Human mAb	In clinical trials
		SCH900222	Human mAb	In clinical trials
	IL-17RA	brodalumab	Human IgG2 mAb	In clinical trials
	IL-17	ixekizumab	Human IgG4 mAb	In clinical trials
		secukinumab	Human IgG1 κ mAb	In clinical trials
Biologics targeting T cells	CD11a	efalizumab	Human IgG1 κ mAb	^a Approved & withdrawn from market
	CD2	alefacept	Fusion protein	^a Approved & withdrawn from market
	CD80, CD86	abatacept	Fusion protein	^b Approved

^a These products have been approved for the treatment of psoriasis

^b These products have been approved for other indication(s) and in clinical trial for psoriasis. *IL* interleukin; *mAb* monoclonal antibody; *PEG* polyethylene glycol; *TNF α* tumor necrosis factor α

classified as IL-12/Th1-mediated inflammatory disorders (5,56). Current understanding is that in psoriasis, activated dendritic cells secrete IL-12 and IL-23 which induce the differentiation of type 1 (Th1) and type 17 (Th17) helper T cells, respectively. Th17 cells in turn secrete cytokines including IL-17 that could activate keratinocytes in the skin (9). Elevated levels of IL-12, IL-23, and IL-17 have all been found in psoriatic lesional skin (57,58). As reported in the product labeling, in a small exploratory study, ustekinumab decreased the expression of mRNA of IL-12 and IL-23 in lesional skin biopsies measured at baseline and up to 2 weeks posttreatment in subjects with psoriasis.

Biologics Targeting T Cells

Although not currently available on the US market due to voluntary withdrawal by the manufacturers, two anti-T cells biologics have been approved for the treatment of psoriasis: efalizumab and alefacept. Efalizumab binds to CD11a, α subunit of leukocyte-function-associated antigen type 1 (LFA-1). Alefacept is a LFA-3/Fc fusion protein targeting CD2. While only approved for the indications of RA and juvenile idiopathic arthritis, abatacept is another anti-T cells biological product, a fusion protein consisting of the extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) linked to a modified Fc.

Psoriasis is characterized by chronic inflammation mediated by T cell activation, differentiation, and migration. T cells also produce cytokines that are essential in psoriasis pathogenesis. The migration of T cells from circulation into dermis and from dermis into epidermis is the key checkpoints in psoriasis (9). As reported in the product labeling, alefacept treatment resulted in a dose-dependent decrease in circulating total lymphocytes which predominantly affected the memory effector subset of the CD4⁺ and CD8⁺ T lymphocytes. In contrast to alefacept, efalizumab inhibits T lymphocyte activation without depleting memory effector T lymphocytes (59,60).

PART 2: PSORIASIS DISEASE-DRUG-DRUG INTERACTIONS

Disease conditions such as inflammation, infection, and cancer are associated with a down-regulation of drug-metabolizing enzymes and transporters (17,61). Psoriasis is a disease condition associated with elevated levels of proinflammatory cytokines (9–15). Overexpression of proinflammatory cytokines under disease condition is known to down-regulate formation and suppress activities of drug-metabolizing enzymes including CYP enzymes. Although direct DDIs between therapeutic proteins and small molecules are unlikely, cytokines or cytokine modulators may indirectly modify the metabolism of small molecule drugs that are substrates for CYP enzymes through their effects on the regulation pathways of the CYP enzymes (16–18). Figure 1 summarizes cytokines that are reported to have the potential to modify the formation, stability, and activity of CYP enzymes and are also involved in the pathogenesis of psoriasis.

Fig. 1. Cytokines associated with psoriasis pathogenesis and potential disease-drug-drug interactions. Cytokines reported to modify CYP enzyme formation, and activities were previously reviewed by Huang *et al.* (16). Pathogenesis of psoriasis involves altered expression of a broad spectrum of proinflammatory and anti-inflammatory cytokines (9–15). *CYP* cytochrome P450; *hGH* human growth hormone; *IFN* interferon; *IL* interleukin; *TNF* tumor necrosis factor

Cytokine Modulation as Pharmacodynamic Effects of Psoriasis Treatments

As discussed in Part 1, anti-cytokines and biologics targeting T cells in psoriasis therapy can have the pharmacodynamic effects of modulating expression levels of multiple cytokines either directly through therapeutic target inhibition or indirectly through improvement of disease condition. For example, the product labeling of TNF α inhibitors (adalimumab, infliximab, and etanercept) reported that they not only down-regulate TNF α levels, but also reduce serum IL-6 level.

Whereas it has been consistently shown that TNF α and IL-6 levels were elevated in psoriasis patients and their expression levels were reduced following biological treatments, literature reports on other cytokines have been inconsistent. For example, IL-7 levels were increased in both the skin and serum of psoriasis patients; however, IL-7 levels did not show clear correlation with the disease severity, nor did they decrease with disease improvement after effective psoriasis treatment with anti-cytokine agents (11). The cytokine alterations associated with psoriasis disease condition appear complex and with some degree of interconnectivity. For example, anti-TNF α therapy was shown to result in rapid decrease in IL-23 levels in psoriasis patients (62,63); on the other hand, ustekinumab (an IL-12/23 inhibitor) improved histological psoriasis measures without affecting serum TNF α level (64).

Recognizing data are available for only a limited number of cytokines, the above examples imply that the disease-DDI for psoriasis could be complicated for a given biologic product. Although these products typically are designed to target one or two specific cytokines, their pharmacodynamic effects could be associated with changes to a more complex cytokine network during treatment. Given the growing knowledge regarding the complexity of inflammatory conditions, the array of pipeline products aiming to treat psoriasis and other inflammatory diseases has expanded beyond those targeting cytokines known to be proinflammatory, e.g., TNF α and IL-6. Nonetheless, modulating inflammatory diseases by various mechanisms of action can be expected to lead to a common outcome of alleviating the inflammatory condition and reducing the levels of proinflammatory cytokines because of the involvement of proinflammatory cytokines in the disease condition. Hence, a holistic approach with *in vivo* studies is more appropriate for investigating the potential effects of psoriasis treatment on the exposure of CYP substrates or disease-DDI. Recently, the scientific community has devoted much attention to the development of *in vitro* models as a tool for evaluating disease-drug interaction. Such efforts are much needed to explore the potential for *in vitro* models to be an integral component of the strategy for evaluating disease-drug-drug interactions although the task may seem daunting.

Current Understanding of Disease-DDI in Rheumatoid Arthritis, an Inflammatory Disease Condition

Rheumatoid arthritis (RA) has been shown to down-regulate CYP enzymes and to affect the exposure of small molecule drug simvastatin. Following the administration of simvastatin (a CYP3A4 substrate), RA patients had a higher

exposure of both simvastatin and its active metabolite, β -hydroxy-simvastatin acid than healthy subjects (18). Additionally, available data suggested that RA disease affected the simvastatin exposure to an extent approximately similar to the effect of coadministered verapamil (a CYP3A4 inhibitor) observed in healthy subjects. For instance, Jacobson *et al.* reported the mean AUC and C_{max} values to be 135 ng*hr/mL and 31 ng/mL, respectively, for a 40 mg dose of simvastatin when coadministered with verapamil in healthy subjects, which were similar to the mean simvastatin AUC and C_{max} values of 105 ng*hr/mL and 36 ng/mL, respectively, in RA patients (18,65). When administered alone at the same dose in healthy subjects, the simvastatin AUC and C_{max} values were 32 ng*hr/mL and 6 ng/mL, respectively (65). These PK data suggest that the RA disease condition may have been associated with a three-fold or greater increase of simvastatin exposure. A three-fold increase in exposure could be large enough to warrant dose adjustment in the case of drugs with narrow therapeutic window; therefore, consideration of the effect of inflammatory disease condition (or disease drug interaction) may be needed in some cases.

Schmitt *et al.* further evaluated RA disease-DDI using tocilizumab, an anti-IL6 receptor monoclonal antibody for RA indication, and simvastatin. A single intravenous infusion of tocilizumab in RA patients was shown to reduce simvastatin AUC by about 60% at 1 week after infusion (18). In comparison, pretreatment with 600 mg rifampin (a CYP3A4 inducer) daily for 5 days resulted in a reduction of simvastatin AUC by 87% (66). Available data reported by Schmitt *et al.* were obtained from a single intravenous dosing of tocilizumab, which could underestimate the maximum extent of interaction given tocilizumab is indicated for chronic treatment and the extent of cytokine modulation can be expected to increase with repeated dosing. However, the maximum extent of disease DDI for tocilizumab in RA patients remains to be defined experimentally.

Assessment of Potential IL-6-Mediated Disease-DDI in Psoriasis

Disease-drug interaction studies have not been conducted in subjects with psoriasis based on our literature review; therefore, the quantitative impacts of psoriasis disease condition on the expression and activity of CYP enzymes or on the PK of CYP substrate drugs are unknown. Similarly, disease-DDI for biological products has not been studied in subjects with psoriasis (67). We believe that a quantitative understanding of the relative expression levels of proinflammatory cytokines between psoriasis patients and healthy subjects may offer insight into the potential for cytokine-mediated disease-drug interaction.

We chose to investigate IL-6 further for the following reasons: (a) IL-6 is considered a marker of the disease activity; (b) reduction of serum IL-6 level has been shown to be a ubiquitous PD response in psoriasis patients treated with biologics such as TNF α inhibitors, adalimumab, infliximab, and etanercept; and (c) the clinical outcome in psoriasis treatment has been shown to be associated with a time- and effect-size-dependent reduction of serum IL-6 level (68,69). Furthermore, given the available disease-DDI

data in RA, comparative profiles of serum IL-6 levels in psoriasis patients *versus* RA patients may allow some understanding of the potential impact of the psoriasis disease condition on CYP enzymes *via* IL-6 modulation as well as the psoriasis disease-DDI potential related to IL-6 modulation.

We reviewed 11 individual reports that contained quantitative measurements of IL-6 levels in psoriasis patients and matched control healthy subjects. Data from these 11 studies were summarized in Table III. While a precise comparison of IL-6 concentrations across studies is not feasible without additional information such as sample handling and assay methodology, a high level impression can be derived. Overall, these studies showed that psoriasis patients had elevated systemic IL-6 levels and the IL-6 levels appeared to be comparable to those reported in RA patients. The mean or median systemic IL-6 concentrations in psoriasis patients ranged from 2.0 to 138.3 pg/mL which represented 1.3- to 12.1-fold of the IL-6 levels in matched control healthy subjects across studies. The average serum IL-6 level observed in RA patients reported by Schmitt *et al.* was 54 pg/mL (18), which was in the range of the mean or median serum IL-6 concentrations in psoriasis patients. At individual subject level, the available data in psoriasis patients showed a wide IL-6 concentration range of 0–764 pg/mL.

It is noteworthy that the serum IL-6 concentrations showed high variability across the 11 studies possibly due to the differences in study locations, the study population,

disease severities, analytical assays used for IL-6 measurements, and other factors. For instance, the psoriasis patients enrolled in the 11 studies had a wide range of the mean PASI scores (4.1 to 44.4) indicating a high variability in disease severities which may contribute to the observed variability in serum IL-6 levels. Furthermore, mean IL-6 levels increased with increasing disease severity according to two studies reported IL-6 data by disease severity, e.g., mild, moderate, and severe (70,71). Based on the IL-6 data, we propose that the potential for psoriasis disease-DDI exist and, therefore, upon initiation of biologics in psoriasis patients who are receiving concomitant CYP substrate with narrow therapeutic window, monitoring of the effect or drug concentration may be useful.

Utilizing the principle of *in vitro*–*in vivo* extrapolation, a physiologically-based pharmacokinetic (PBPK) model was recently established to describe the quantitative relationship between elevated levels of IL-6, hepatic CYP3A4 activity, and PK of simvastatin in RA patients (72). According to the PBPK model-based simulations, the IL-6-mediated CYP3A activity regulation was negligible when the IL-6 concentrations were less than 10 pg/mL, while the CYP3A activity was significantly suppressed when the IL-6 concentrations were increased to above 50 pg/mL. If we were to use 10 and 50 pg/mL as the benchmarks, data in Table III would support that the IL-6-mediated disease-DDI in psoriasis could not be dismissed. However, inferences drawn from cross-study comparisons should be deemed as a call for

Table III. Elevated Levels of Systemic IL-6 Expression in Subjects with Psoriasis. Serum or plasma IL-6 concentrations in psoriasis patients showed 1.3- to 12.1-fold of the levels in matched control healthy subjects across different studies. While intra-study comparison showed good correlation between PASI Scores and IL-6 expression levels, no significant correlation across different studies was observed due to the variability of the data. The variability of the data could be resulted from the differences in study population, analytical assays used for IL-6 measurements and other unknown factors

Study location	PASI in psoriasis patients (mean±SD)	Serum IL-6 levels							References
		Psoriasis patients (Ps)			Healthy subjects (HS)			Ratio [#] (Ps/HS)	
		n values	mean±SD	range	n	mean±SD	range		
Estonia ^a	13.4±6.8	22	2.0±1.02	n/a	22	1.5±0.8	n/a	1.3	(78)
India	22.3±10.6	22	15.9±4.5	10–22	20	5.5±1.3	n/a	2.9	(69)
Italy ^b	Severe	26	7.8±5.0	n/a	25	2.1±0.8	n/a	3.7	(71)
	Mild	18	3.4±1.6	n/a				1.6	
Greece	4.1±3.3	20	24.6±16.1	n/a	45	4.9±3.8	n/a	5.0	(79)
Japan ^c	9.3±3.7	122	3.2±0.8	n/a	78	1.8±0.2	n/a	1.8	(80)
Japan ^d	1–50	30	13.4±4.7	n/a	30	2.9±0.5	n/a	4.6	(81)
Poland	16.7±5.7	106	4*	0–305	40	1*	0–7	4.0	(82)
Poland	26.0±10.9	40	6.4±6.5	0–24	18	1.5±1.2	0–5	4.3	(83)
Sweden ^e	8.5 (2.0–25.3)	14	138.31	2–764	14	30.59	2–222	4.5	(84)
Turkey	9.3±8.2	30	13.7±12.2	0–62.0	23	4.2±5.9	0–12.7	3.3	(85)
United Arab Emirates	6.6±1.1 (mild)	24	47.3±1.2	n/a	10	6.6±0.9	n/a	7.2	(70)
	22.5±1.4 (moderate)	9	56.4±2.2	n/a				8.5	
	44.4±6.2 (severe)	5	80.0±5.1	n/a				12.1	

^a PASI values were derived from two subgroups with mean±SD values of 14.5±6.5 (*n*=10) and 12.4±7.1 (*n*=12), respectively

^b The PASI scores in psoriatic patients had a range of 3–33.4

^c PASI values were derived from two subgroups of 81 male (PASI=10.5±3.5) and 41 female (PASI=6.8±2.8)

^d The PASI score was estimated from the data plot in the referenced article

^e The PASI values were reported as mean (and range)

[#] The ratio was calculated as the mean or median value of the IL-6 level in psoriasis patients divided by the level in the matched control healthy subjects

*The values were reported as median. *n/a* not available; *PASI* psoriasis area and severity index

further investigation because a precise and quantitative comparison would require further understanding of the methodology used in determining IL-6 concentrations in various studies as well as in the source study(ies) supported the establishment of the PBPK database.

PART 3 STUDY DESIGN CONSIDERATIONS FOR PSORIASIS DISEASE-DDI CLINICAL TRIALS

Because the nature of disease-DDI involves the disease conditions (i.e., associated with elevated proinflammatory cytokines and suppressed CYP activity) and possibly the treatment responses (i.e., associated with normalization of cytokine levels and CYP activity), the study design considerations for clinical disease-DDI studies with biological products differ from those of conventional studies for DDI between two small molecule drug products. We highlight some particular considerations for clinical evaluations of psoriasis disease-DDI from the clinical pharmacology perspectives including study population, dosing regimen, and probe drugs.

Study Population

The indicated patient population would be an appropriate study population to assess the extent of disease-DDI and to inform clinical practice. For instance, adult subjects with moderate-to-severe plaque psoriasis could be the study population to investigate psoriasis disease-DDI with currently approved biological products. The investigation of disease-DDI requires the collection of the exposure data for CYP substrate drugs in the target population before and after biological therapies to determine whether the treatment-induced disease improvement has an impact. Clinical studies are necessary because *in vitro* or animal studies have limited value in the qualitative and quantitative projection of clinical interactions, and the translation of results from *in vitro* to *in vivo* and from animal to human has been inconsistent (73).

From a scientific perspective, healthy subjects would not be an appropriate population for investigating disease-DDI as they do not have the perturbed cytokines network reflective of the disease condition. Additionally, a subset of the indicated patients with the most severe condition would conceivably be the appropriate study population as they may have the greatest perturbation of cytokines and CYP suppression. As such, administration of biologic products may produce the greatest change in cytokine levels and the CYP activity in these subjects. Therefore, data from such a subset study may permit the assessment of the maximum extent of change in the exposure of CYP substrate upon treatment. An established relationship between the disease severity and the extent of cytokine elevation, and CYP suppression would lend further support to the use of a subset of target population.

Dosing Regimen

The recommended dosing regimen for an approved biological product would be appropriate for a psoriasis disease-DDI study. A study with a single dose of the biological product of interest can demonstrate that the treatment affects the exposure of victim drug (CYP substrate

drug), i.e., the presence of disease-DDI as shown in the RA disease-DDI example where tocilizumab affected simvastatin exposure (18). Because biological products typically have a long half-life, the CYP substrate drug can be administered at more than one time point after a single dose of biological product to evaluate the time-dependent potential of the disease-DDI. For instance, a single dose of tocilizumab reduced the exposure of simvastatin in a time-dependent manner (57% at 1 week and 39% at 5 weeks after tocilizumab administration) in RA patients, which could be due to a time-dependent effect or concentration-dependent effect of tocilizumab on the reversal of CYP3A4 suppression (18). While it was not evaluated in the above mentioned study, a greater reduction of simvastatin exposure can be expected following repeated dosing of tocilizumab because RA disease improvement may occur gradually and requires multiple dose treatment to show the full extent of disease-DDI.

The same principle would apply to psoriasis disease-DDI studies. As the psoriasis disease improvement progresses over time during a biological therapy, the magnitude of treatment-induced modulation of cytokine expression levels and normalization of CYP enzyme activities are also likely to increase over time. Results from a study with a single dose of biological treatment may not be reflective of the extent of disease-DDI in patients receiving chronic treatment and eventually achieving the desired therapeutic effects at a pharmacodynamic steady state for the given treatment regimen. Therefore, a study with repeated doses of the biological product of interest at the approved dose regimen (dose and dosing frequency) would be more informative in defining the disease-DDI in clinical practice.

Probe Drugs

The utility of simvastatin as a probe substrate for CYP3A4 was demonstrated in the RA disease-DDI study (18). However, multiple CYP substrate drugs (victim drugs) may need to be evaluated in psoriasis disease-DDI studies because of the complexity of the cytokine network involved in psoriasis disease condition and the treatment-induced improvements which may have impact on multiple CYP enzymes. The selection of appropriate CYP substrate drugs is important for the clinical investigation of disease-DDI. For the specific probe drug choices, we refer the readers to abundant literature resources for guidance (73,74). Given multiple CYP probe drugs of interest, the cocktail approach could be a reasonable strategy.

Other Considerations

Because psoriasis disease condition is associated with elevated levels of proinflammatory cytokines and the treatment effects of biological agents include the reduction of the levels of proinflammatory cytokines, it is possible that the extent of disease-DDI could be dependent on the extent of treatment effect (e.g., varying degrees of cytokine modulation and disease improvement) and may differ between responders and non-responders. As such, psoriasis disease-DDI evaluated in a clinical trial where clinical efficacy data could be obtained to distinguish responders from non-responders to the biological therapy may offer additional insight of disease-DDI. Inclusion

	Inflammatory disease state (e.g., psoriasis)	Healthy state	Disease relapse or rebound
Pro-inflammatory cytokine expression	Elevated	Normalized	Elevated
CYP Enzymes expression and activity	Suppressed	Normalized	Suppressed
CYP substrate exposure			

Fig. 2. Cytokine-mediated disease-DDI in inflammatory disease conditions (e.g., psoriasis). Proinflammatory cytokines are overexpressed under an inflammatory disease condition such as psoriasis. Elevated levels of cytokines down-regulate the formation, stability, and activity of drug-metabolizing enzymes including cytochrome P450 enzymes (CYP), which in turn result in increased exposure of CYP substrate. Following biological treatment and disease condition improvement, the exposure of the CYP substrate is normalized to that in healthy subjects (assuming that maximal treatment effect induces complete normalization of cytokine levels into healthy state). In the event of disease return (relapse) or worsening (rebound) when the biological therapy is discontinued or even during the treatment, reelevated levels of cytokines result in CYP enzymes inhibition and increased exposure of small molecule drugs. In the event of the disease rebound, the exposure of the CYP substrate could be even higher than that before the initiation of the biological treatment due to worsening of the disease (see text). In situations of disease relapse or rebound, and when new therapies are reinitiated, patients who are receiving concomitant CYP substrate, monitoring of the effect or drug concentration is needed, particularly for CYP substrates with narrow therapeutic index where the dose is individually adjusted

of measurements of cytokine levels in addition to assessment of DDI and clinical efficacy would be very helpful to the data interpretation. Figure 2 shows examples of cytokine-mediated disease-DDI in inflammatory disease conditions (e.g., psoriasis) by illustrating schematic relationships among the expression levels of proinflammatory cytokines, the activity of drug-metabolizing enzyme CYP, and the PK exposure of CYP substrate.

Currently available biological therapies for psoriasis are not curative and their PD effects are reversible (75). Return (relapse) or worsening (rebound) of the disease could occur when a therapy is discontinued or even during the treatment (76,77), which will require initiation of alternative therapies. Disease return or rebound could be associated with elevated cytokine expressions and CYP enzymes inhibition, possibly to a greater extent than the pretreatment state, resulting in increased exposure of small molecule drugs. The impact of disease relapse or rebound on exposure of CYP substrates is a special case where disease-DDI investigation could be relevant scientifically and clinically. To evaluate the effects of disease relapse or rebound, it is more practical to conduct a study in a cohort of subjects meeting the disease relapse/rebound criteria, as opposed to building it into Phase 3 trials. Insights regarding the necessity of such a targeted study could be gained by obtaining PD data and biomarker information such as cytokine level changes in patients with disease relapse or rebound in a larger trial setting (such as Phase 3 trials).

PART 4: CONCLUSIONS AND PERSPECTIVES

The introduction of targeted biologic therapies has greatly improved the treatment options for psoriasis although the pathogenesis of the autoimmune skin disease has not

been fully elucidated. The potential for psoriasis disease-DDI is implicit because altered expressions of cutaneous and systemic cytokines are well demonstrated in psoriasis patients. In particular, the elevated proinflammatory cytokines in psoriasis patients can suppress CYP enzymes and the disease improvement can be associated with a reversal of CYP enzyme suppression resulting in disease-DDI. The potential consequences of disease-DDI include a reduction of systemic exposure and thus reduced efficacy of drugs that are substrates of impacted CYP enzymes.

A simple psoriasis disease-drug interaction study (to evaluate the disease impact on PK of CYP substrate drugs) would pave the way for addressing the more complicated psoriasis disease-DDI when biological therapies are involved. Psoriasis disease-DDI investigation may not be necessary if the extents to which the psoriasis disease condition affects the exposures of CYP substrate drugs are found not clinically meaningful. In other words, if the inflammatory disease condition, psoriasis, does not suppress the CYP enzymes to a clinically meaningful extent, an improvement on psoriasis condition after treatment with a biologic agent would not be expected to significantly alter the exposures of CYP substrates. On the other hand, if psoriasis disease condition has a clinically meaningful impact on the exposure of CYP substrate drugs, further investigation of disease-DDI would be important for biologics in psoriasis treatment.

Findings from our literature review revealed that psoriasis patients had elevated systemic IL-6 levels compared to the matched healthy control subjects and suggested the IL-6-mediated disease-DDI in psoriasis patients may not be dismissed. In addition to IL-6, other proinflammatory cytokines can be elevated and also contribute to the disease-DDI in psoriasis; therefore, a holistic approach of disease-DDI evaluation carried out *in vivo* in psoriasis patients would be more

appropriate. Efforts in developing *in vitro* models may someday produce useful tools to be integrated into the disease-DDI evaluation strategy. One publication has shown PBPK modeling approach to be successful in describing the impact of IL-6 on CYP activity, suggesting that modeling approach may be useful in integrating data to describe complex cytokine-driven CYP enzyme modulations. Data on more cytokine biomarkers relevant to disease conditions of interest are needed to enrich the knowledgebase and facilitate further development of advanced computational approach for *in silico* prediction of the disease-DDI potential for new biological therapeutics.

ACKNOWLEDGMENTS

The authors wish to thank Dr. E. Dennis Bashaw for his critical review of this manuscript and valuable comments.

REFERENCES

- Christophers E. Psoriasis—epidemiology and clinical spectrum. *Clin Exp Dermatol*. 2001;26(4):314–20.
- Sivamani RK, Goodarzi H, Garcia MS, Raychaudhuri SP, Wehrli LN, Ono Y, et al. Biologic Therapies in the Treatment of Psoriasis: A Comprehensive Evidence-Based Basic Science and Clinical Review and a Practical Guide to Tuberculosis Monitoring. *Clin Rev Allergy Immunol* 2012 Feb 5.
- Perera GK, Di MP, Nestle FO. Psoriasis. *Annu Rev Pathol*. 2012;7:385–422.
- Nijsten T, Margolis DJ, Feldman SR, Rolstad T, Stern RS. Traditional systemic treatments have not fully met the needs of psoriasis patients: Results from a national survey. *J Am Acad Dermatol*. 2005;52(3 Pt 1):434–44.
- Kupetsky EA, Mathers AR, Ferris LK. Anti-cytokine therapy in the treatment of psoriasis. *Cytokine*. 2013;61(3):704–12.
- Ryan C, Abramson A, Patel M, Menter A. Current investigational drugs in psoriasis. *Expert Opin Investig Drugs*. 2012;21(4):473–87.
- Lew W, Bowcock AM, Krueger JG. Psoriasis vulgaris: cutaneous lymphoid tissue supports T-cell activation and “Type 1” inflammatory gene expression. *Trends Immunol*. 2004;25(6):295–305.
- Sivamani RK, Correa G, Ono Y, Bowen MP, Raychaudhuri SP, Mavarakis E. Biological therapy of psoriasis. *Indian J Dermatol*. 2010;55(2):161–70.
- Nestle FO, Kaplan DH, Barker J. Psoriasis. *N Engl J Med*. 2009;361(5):496–509.
- Nograles KE, Krueger JG. Anti-cytokine therapies for psoriasis. *Exp Cell Res*. 2011;317(9):1293–300.
- Pietrzak AT, Zalewska A, Chodorowska G, Krasowska D, Michalak-Stoma A, Nockowski P, et al. Cytokines and anticytokines in psoriasis. *Clin Chim Acta*. 2008;394(1–2):7–21.
- Asadullah K, Docke WD, Ebeling M, Friedrich M, Belbe G, Audring H, et al. Interleukin 10 treatment of psoriasis: clinical results of a phase 2 trial. *Arch Dermatol*. 1999;135(2):187–92.
- Salim A, Emerson R. Targeting interleukin-2 as a treatment for psoriasis. *Curr Opin Investig Drugs*. 2001;2(11):1546–8.
- Zheng Y, Danilenko DM, Valdez P, Kasman I, Eastham-Anderson J, Wu J, et al. Interleukin-22, a T(H)17 cytokine, mediates IL-23-induced dermal inflammation and acanthosis. *Nature*. 2007;445(7128):648–51.
- Tohyama M, Yang L, Hanakawa Y, Dai X, Shirakata Y, Sayama K. IFN- α enhances IL-22 receptor expression in keratinocytes: a possible role in the development of psoriasis. *J Invest Dermatol*. 2012;132(7):1933–5.
- Huang SM, Zhao H, Lee JI, Reynolds K, Zhang L, Temple R, et al. Therapeutic protein-drug interactions and implications for drug development. *Clin Pharmacol Ther*. 2010;87(4):497–503.
- Morgan ET. Impact of infectious and inflammatory disease on cytochrome P450-mediated drug metabolism and pharmacokinetics. *Clin Pharmacol Ther*. 2009;85(4):434–8.
- Schmitt C, Kuhn B, Zhang X, Kivitz AJ, Grange S. Disease-drug-drug interaction involving tocilizumab and simvastatin in patients with rheumatoid arthritis. *Clin Pharmacol Ther*. 2011;89(5):735–40.
- Garcia-Valladares I, Cuchacovich R, Espinoza LR. Comparative assessment of biologics in treatment of psoriasis: Drug design and clinical effectiveness of ustekinumab. *Drug Des Devel Ther*. 2011;5:41–9.
- Leonardi CL, Kimball AB, Papp KA, Yeilding N, Guzzo C, Wang Y, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). *Lancet*. 2008;371(9625):1665–74.
- Papp KA, Langley RG, Lebwohl M, Krueger GG, Szapary P, Yeilding N, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). *Lancet*. 2008;371(9625):1675–84.
- Di MP, Nestle FO. The role of IL-23 in the immunopathogenesis of psoriasis. *F1000 Biol Rep* 2010;2.
- Tonel G, Conrad C, Laggner U, Di MP, Grys K, McClanahan TK, et al. Cutting edge: a critical functional role for IL-23 in psoriasis. *J Immunol*. 2010;185(10):5688–91.
- Hueber W, Patel DD, Dryja T, Wright AM, Koroleva I, Bruin G, et al. Effects of AIN457, a fully human antibody to interleukin-17A, on psoriasis, rheumatoid arthritis, and uveitis. *Sci Transl Med*. 2010;2(52):52ra72.
- Papp KA, Reid C, Foley P, Sinclair R, Salinger DH, Williams G, et al. Anti-IL-17 Receptor Antibody AMG 827 Leads to Rapid Clinical Response in Subjects with Moderate to Severe Psoriasis: Results from a Phase I, Randomized, Placebo-Controlled Trial. *J Invest Dermatol* 2012 May 24.
- Martin DA, Towne JE, Kricorian G, Klekotka P, Gudjonsson JE, Krueger JG, et al. The Emerging Role of IL-17 in the Pathogenesis of Psoriasis: Preclinical and Clinical Findings. *J Invest Dermatol* 2012 Jun 7.
- Weger W. Current status and new developments in the treatment of psoriasis and psoriatic arthritis with biological agents. *Br J Pharmacol*. 2010;160(4):810–20.
- Al-Hoqail IA. Personalized medicine in psoriasis: Concept and applications. *Curr Vasc Pharmacol*. 2010;8(3):432–6.
- de Vlam K, Gottlieb AB, Fitzgerald O. Biological biomarkers in psoriatic disease. A review. *J Rheumatol*. 2008;35(7):1443–8.
- Enerback C. Soluble biomarkers in psoriasis. *Eur J Dermatol*. 2011;21(6):844–50.
- Flisiak I, Zaniewski P, Chodnicka B. Plasma TGF- β 1, TIMP-1, MMP-1 and IL-18 as a combined biomarker of psoriasis activity. *Biomarkers*. 2008;13(5):549–56.
- Prieto-Perez R, Cabaleiro T, Dauden E, Abad-Santos F. Gene polymorphisms that can predict response to anti-TNF therapy in patients with psoriasis and related autoimmune diseases. *Pharmacogenomics J*. 2013;13(4):297–305.
- Rashmi R, Rao KS, Basavaraj KH. A comprehensive review of biomarkers in psoriasis. *Clin Exp Dermatol*. 2009;34(6):658–63.
- Sandborn WJ, Feagan BG, Stoinov S, Honiball PJ, Rutgeerts P, Mason D, et al. Certolizumab pegol for the treatment of Crohn's disease. *N Engl J Med*. 2007;357(3):228–38.
- Pappas DA, Bathon JM, Hanicq D, Yasothan U, Kirkpatrick P. Golimumab. *Nat Rev Drug Discov*. 2009;8(9):695–6.
- Tracey D, Klareskog L, Sasso EH, Salfeld JG, Tak PP. Tumor necrosis factor antagonist mechanisms of action: a comprehensive review. *Pharmacol Ther*. 2008;117(2):244–79.
- Reich K, Ortonne JP, Gottlieb AB, Terpstra JJ, Coteur G, Tasset C, et al. Successful treatment of moderate to severe plaque psoriasis with the PEGylated Fab' certolizumab pegol: Results of a phase II randomized, placebo-controlled trial with a re-treatment extension. *Br J Dermatol*. 2012;167(1):180–90.
- Horiuchi T, Mitoma H, Harashima S, Tsukamoto H, Shimoda T. Transmembrane TNF- α : Structure, function and interaction with anti-TNF agents. *Rheumatology (Oxford)*. 2010;49(7):1215–28.

39. Schottelius AJ, Moldawer LL, Dinarello CA, Asadullah K, Sterry W, Edwards III CK. Biology of tumor necrosis factor- α -implications for psoriasis. *Exp Dermatol*. 2004;13(4):193–222.
40. Mussi A, Bonifati C, Carducci M, D'Agosto G, Pimpinelli F, D'Urso D, *et al.* Serum TNF- α levels correlate with disease severity and are reduced by effective therapy in plaque-type psoriasis. *J Biol Regul Homeost Agents*. 1997;11(3):115–8.
41. Soegaard-Madsen L, Johansen C, Iversen L, Kragballe K. Adalimumab therapy rapidly inhibits p38 mitogen-activated protein kinase activity in lesional psoriatic skin preceding clinical improvement. *Br J Dermatol*. 2010;162(6):1216–23.
42. Caproni M, Antiga E, Melani L, Volpi W, Del BE, Fabbri P. Serum levels of IL-17 and IL-22 are reduced by etanercept, but not by acitretin, in patients with psoriasis: a randomized-controlled trial. *J Clin Immunol*. 2009;29(2):210–4.
43. Reddy M, Davis C, Wong J, Marsters P, Pendley C, Prabhakar U. Modulation of CLA, IL-12R, CD40L, and IL-2R α expression and inhibition of IL-12- and IL-23-induced cytokine secretion by CNTO 1275. *Cell Immunol*. 2007;247(1):1–11.
44. Gottlieb AB, Goldminz AM. Ustekinumab for psoriasis and psoriatic arthritis. *J Rheumatol Suppl*. 2012 Jul;89:86–9.
45. Traczewski P, Rudnicka L. Briakinumab for the treatment of plaque psoriasis. *BioDrugs*. 2012;26(1):9–20.
46. Lowes MA, Russell CB, Martin DA, Towne JE, Krueger JG. The IL-23/Th17 pathogenic axis in psoriasis is amplified by keratinocyte responses. *Trends Immunol*. 2013;34(4):174–81.
47. Di MP, Nestle FO. The role of IL-23 in the immunopathogenesis of psoriasis. *F1000 Biol Rep*. 2010;2.
48. Papp KA, Reid C, Foley P, Sinclair R, Salinger DH, Williams G, *et al.* Anti-IL-17 Receptor Antibody AMG 827 Leads to Rapid Clinical Response in Subjects with Moderate to Severe Psoriasis: Results from a Phase I, Randomized, Placebo-Controlled Trial. *J Invest Dermatol*. 2012 May 24.
49. Leonardi C, Matheson R, Zachariae C, Cameron G, Li L, Edson-Heredia E, *et al.* Anti-interleukin-17 monoclonal antibody ixekizumab in chronic plaque psoriasis. *N Engl J Med*. 2012;366(13):1190–9.
50. Hueber W, Patel DD, Dryja T, Wright AM, Koroleva I, Bruin G, *et al.* Effects of AIN457, a fully human antibody to interleukin-17A, on psoriasis, rheumatoid arthritis, and uveitis. *Sci Transl Med*. 2010;2(52):52ra72.
51. Papp KA, Leonardi C, Menter A, Ortonne JP, Krueger JG, Kricorian G, *et al.* Brodalumab, an anti-interleukin-17-receptor antibody for psoriasis. *N Engl J Med*. 2012;366(13):1181–9.
52. Waisman A. To be 17 again—anti-interleukin-17 treatment for psoriasis. *N Engl J Med*. 2012;366(13):1251–2.
53. Gandhi M, Alwawi E, Gordon KB. Anti-p40 antibodies ustekinumab and briakinumab: Blockade of interleukin-12 and interleukin-23 in the treatment of psoriasis. *Semin Cutan Med Surg*. 2010;29(1):48–52.
54. Di CA, Di MP, Nestle FO. The IL-23/Th17 axis in the immunopathogenesis of psoriasis. *J Invest Dermatol*. 2009;129(6):1339–50.
55. Wilson NJ, Bonifati K, Chan JR, McKenzie BS, Blumenschein WM, Mattson JD, *et al.* Development, cytokine profile and function of human interleukin 17-producing helper T cells. *Nat Immunol*. 2007;8(9):950–7.
56. van Beelen AJ, Teunissen MB, Kapsenberg ML, de Jong EC. Interleukin-17 in inflammatory skin disorders. *Curr Opin Allergy Clin Immunol*. 2007;7(5):374–81.
57. Lee E, Trepicchio WL, Oestreicher JL, Pittman D, Wang F, Chamian F, *et al.* Increased expression of interleukin 23 p19 and p40 in lesional skin of patients with psoriasis vulgaris. *J Exp Med*. 2004;199(1):125–30.
58. Shaker OG, Moustafa W, Essmat S, Abdel-Halim M, El-Komy M. The role of interleukin-12 in the pathogenesis of psoriasis. *Clin Biochem*. 2006;39(2):119–25.
59. Krueger GG. Selective targeting of T cell subsets: focus on alefacept—a remittive therapy for psoriasis. *Expert Opin Biol Ther*. 2002;2(4):431–41.
60. Lebwohl M, Tying SK, Hamilton TK, Toth D, Glazer S, Tawfik NH, *et al.* A novel targeted T-cell modulator, efalizumab, for plaque psoriasis. *N Engl J Med*. 2003;349(21):2004–13.
61. Aitken AE, Richardson TA, Morgan ET. Regulation of drug-metabolizing enzymes and transporters in inflammation. *Annu Rev Pharmacol Toxicol*. 2006;46:123–49.
62. Zaba LC, Suarez-Farinas M, Fuentes-Duculan J, Nogales KE, Guttman-Yassky E, Cardinale I, *et al.* Effective treatment of psoriasis with etanercept is linked to suppression of IL-17 signaling, not immediate response TNF genes. *J Allergy Clin Immunol*. 2009;124(5):1022–10.
63. Zaba LC, Cardinale I, Gilleaudeau P, Sullivan-Whalen M, Suarez-Farinas M, Fuentes-Duculan J, *et al.* Amelioration of epidermal hyperplasia by TNF inhibition is associated with reduced Th17 responses. *J Exp Med*. 2007;204(13):3183–94.
64. Reddy M, Torres G, McCormick T, Marano C, Cooper K, Yeilding N, *et al.* Positive treatment effects of ustekinumab in psoriasis: analysis of lesional and systemic parameters. *J Dermatol*. 2010;37(5):413–25.
65. Jacobson TA. Comparative pharmacokinetic interaction profiles of pravastatin, simvastatin, and atorvastatin when coadministered with cytochrome P450 inhibitors. *Am J Cardiol*. 2004;94(9):1140–6.
66. Kyrklund C, Backman JT, Kivisto KT, Neuvonen M, Laitila J, Neuvonen PJ. Rifampin greatly reduces plasma simvastatin and simvastatin acid concentrations. *Clin Pharmacol Ther*. 2000;68(6):592–7.
67. Gupta R, Levin E, Wu JJ, Koo J, Liao W. An update on drug-drug interactions with biologics for the treatment of moderate-to-severe psoriasis. *J Dermatolog Treat*. 2013 Aug 27.
68. Grossman RM, Krueger J, Yourish D, Granelli-Piperno A, Murphy DP, May LT, *et al.* Interleukin 6 is expressed in high levels in psoriatic skin and stimulates proliferation of cultured human keratinocytes. *Proc Natl Acad Sci U S A*. 1989;86(16):6367–71.
69. Elango T, Dayalan H, Subramanian S, Gnanaraj P, Malligarjunan H. Serum interleukin-6 levels in response to methotrexate treatment in psoriatic patients. *Clin Chim Acta*. 2012;413(19–20):1652–6.
70. Galadari I, Sheriff MO. Estimation of interleukin-6 level in psoriasis patients. *Eur Ann Allergy Clin Immunol*. 2005;37(2):63–5.
71. Bevelacqua V, Libra M, Mazzarino MC, Gangemi P, Nicotra G, Curatolo S, *et al.* Long pentraxin 3: a marker of inflammation in untreated psoriatic patients. *Int J Mol Med*. 2006;18(3):415–23.
72. Machavaram KK, Almond LM, Rostami-Hodjegan A, Gardner I, Jamei M, Tay S, *et al.* A physiologically based pharmacokinetic modeling approach to predict disease-drug interactions: Suppression of CYP3A by IL-6. *Clin Pharmacol Ther*. 2013;94(2):260–8.
73. Drug interaction studies – study design, data analysis, implications for dosing, and labeling recommendations. FDA Guidance for Industry (Draft) 2012 Feb.
74. Sinz M, Wallace G, Sahi J. Current industrial practices in assessing CYP450 enzyme induction: preclinical and clinical. *AAPS J*. 2008;10(2):391–400.
75. Johnson-Huang LM, Pensabene CA, Shah KR, Pierson KC, Kikuchi T, Lentini T, *et al.* Post-therapeutic relapse of psoriasis after CD11a blockade is associated with T cells and inflammatory myeloid DCs. *PLoS ONE*. 2012;7(2):e30308.
76. Carey W, Glazer S, Gottlieb AB, Lebwohl M, Leonardi C, Menter A, *et al.* Relapse, rebound, and psoriasis adverse events: an advisory group report. *J Am Acad Dermatol*. 2006;54(4 Suppl 1):S171–81.
77. Leonardi C, Langley RG, Papp K, Tying SK, Wasel N, Vender R, *et al.* Adalimumab for treatment of moderate to severe chronic plaque psoriasis of the hands and feet: efficacy and safety results from REACH, a randomized, placebo-controlled, double-blind trial. *Arch Dermatol*. 2011;147(4):429–36.
78. Kaur S, Zilmer K, Kairane C, Kals M, Zilmer M. Clear differences in adiponectin level and glutathione redox status revealed in obese and normal-weight patients with psoriasis. *Br J Dermatol*. 2008;159(6):1364–7.
79. Vasilopoulos Y, Sourli F, Zafiriou E, Klimi E, Ioannou M, Mamuris Z, *et al.* High serum levels of HIF-1 α in psoriatic

- patients correlate with an over-expression of IL-6. Cytokine. 2013;62(1):38–9.
80. Takahashi H, Tsuji H, Hashimoto Y, Ishida-Yamamoto A, Iizuka H. Serum cytokines and growth factor levels in Japanese patients with psoriasis. Clin Exp Dermatol. 2010;35(6):645–9.
81. Nakajima H, Nakajima K, Tarutani M, Morishige R, Sano S. Kinetics of circulating Th17 cytokines and adipokines in psoriasis patients. Arch Dermatol Res. 2011;303(6):451–5.
82. Zalewska A, Glowacka E, Wyczolkowska J, Tchorzewski H, Narbutt J, Sysa-Jedrzejowska A. Interleukin 6 and 8 levels in plasma and fibroblast cultures in psoriasis. Mediat Inflamm. 2006;2006(1):81767.
83. Szepietowski JC, Bielicka E, Nockowski P, Noworolska A, Wasik F. Increased interleukin-7 levels in the sera of psoriatic patients: Lack of correlations with interleukin-6 levels and disease intensity. Clin Exp Dermatol. 2000;25(8):643–7.
84. Anderson KS, Petersson S, Wong J, Shubbar E, Lokko NN, Carlstrom M, *et al.* Elevation of serum epidermal growth factor and interleukin 1 receptor antagonist in active psoriasis vulgaris. Br J Dermatol. 2010;163(5):1085–9.
85. Arican O, Aral M, Sasmaz S, Ciragil P. Serum levels of TNF-alpha, IFN-gamma, IL-6, IL-8, IL-12, IL-17, and IL-18 in patients with active psoriasis and correlation with disease severity. Mediat Inflamm. 2005;2005(5):273–9.