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A mathematical model to identify optimal combinations of drug targets for dupilumab poor responders in atopic dermatitis

(Short title: Simulated efficacy for dupilumab poor responders in AD)

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Conflict of Interest statement

Takuya Miyano reports personal fees from DAIICHI SANKYO CO., LTD., during the conduct of the study, outside the submitted work; Alan D Irvine reports personal fees from Sanofi Regeneron, personal fees from Abbvie, personal fees from Eli Lilly, personal fees from Pfizer, personal fees from UCB Pharma, personal fees from Novartis, personal fees from Dermavant, personal fees from Benevolent AI, personal fees from Menlo Therapeutics, personal fees from Chugai, personal fees from LEO Pharma, personal fees from Arena, during the conduct of the study; Reiko J Tanaka reports grants from British Skin Foundation, during the conduct of the study.

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TM and RJT designed the research and wrote the article. TM performed the research and analyzed the data. TM, ADI and RJT contributed to review and approval of the manuscript.

Abstract

Background: Several biologics for atopic dermatitis (AD) have demonstrated good efficacy in clinical trials, but with a substantial proportion of patients being identified as poor responders. This study aims to understand the pathophysiological backgrounds of patient variability in drug response, especially for dupilumab, and to identify promising drug targets in dupilumab poor responders.

Methods: We conducted model-based meta-analysis of recent clinical trials of AD biologics and developed a mathematical model that reproduces reported clinical efficacies for nine biological drugs (dupilumab, lebrikizumab, tralokinumab, secukinumab, fezakinumab, nemolizumab, tezepelumab, GBR 830, and recombinant interferon-gamma) by describing systems-level AD pathogenesis. Using this model, we simulated the clinical efficacy of hypothetical therapies on virtual patients.

Results: Our model reproduced reported time courses of %improved EASI and EASI-75 of the nine drugs. The global sensitivity analysis and model simulation indicated the baseline level of IL-13 could stratify dupilumab good responders. Model simulation on the efficacies of hypothetical therapies revealed that simultaneous inhibition of IL-13 and IL-22 was effective, whereas application of the nine biologic drugs was ineffective, for dupilumab poor responders (EASI-75 at 24 weeks: 21.6% vs. max. 1.9%).

Conclusion: Our model identified IL-13 as a potential predictive biomarker to stratify dupilumab good responders, and simultaneous inhibition of IL-13 and IL-22 as a promising drug therapy for dupilumab poor responders. This model will serve as a computational platform for model-informed drug development for precision medicine, as it allows evaluation of the effects of new potential drug targets and the mechanisms behind patient variability in drug response.

KEYWORDS

atopic dermatitis, dupilumab, model-based meta-analysis, poor responders, quantitative systems pharmacology

1. INTRODUCTION

Atopic dermatitis (AD) is the most common inflammatory skin disease, whose incidence is increasing in many areas of the world, especially urbanized areas, with a current worldwide prevalence of 5%-25%¹. Primary symptoms of AD are relapsing pruritus and skin pain, impairing patients' quality of life, for example by sleep disturbance and decreased work productivity especially in moderate-to-severe cases². The pathogenesis of AD involves epidermal barriers abnormalities, dysbiosis and heterogeneous immunological dysregulations^{3,4,5} characterized by a dominant Type 2 immune activation including the T helper (Th) 2 axis and, depending on the lesional stage and ethnicity, varying degrees of upregulation of the Th1, Th17, and Th22 axes. These Th cells produce inflammatory cytokines such as interleukin (IL)-4, IL-13, IL-17A, IL-22, and IL-31, all of which have been identified and investigated as therapeutic targets for AD^{4,5}.

Dupilumab, a monoclonal antibody that inhibits signaling from IL-4 and IL-13 by blocking their common IL-4 receptor subunit α (IL-4R α), was approved as the first and, so far, the only AD-specific biologic in 2017⁶ for its promising efficacy demonstrated in clinical trials. The high efficacy of dupilumab confirmed the clinical validity of IL-4 and IL-13 as therapeutic targets for AD. However, dupilumab treatment was not effective for a sub-population of patients; the responder rates for dupilumab remain 44%-69% for Eczema Area and Severity Index (EASI)-75 (75% reduction in the EASI score^{7, 8}) and 36%-39% for achievement of clear or almost clear skin in Investigator's Global Assessment, respectively^{9, 10}.

A significant percentage of poor responders was also observed for investigational drugs with other mechanisms of action (MoA), even if their clinical efficacy was confirmed for the study population average. It is thus of high clinical importance to identify underlying

pathogenesis that causes the patients' variability in responsiveness to each drug, and to investigate whether there are alternative drug targets for those poor responders.

The clinical efficacy of investigational drugs for AD have been evaluated in many clinical trials. Reviewing the combined results from the clinical trials, for example by network meta-analysis¹¹, suggested hypothetical AD pathogenesis described as diagrammatic pathways^{12, 13}. However, such a qualitative framework does not account for patient stratification and for development of drugs that can be effective for poor responders to existing drugs, because underlying mechanisms for the variability in individual patients' responsiveness cannot be evaluated. In addition, a simple correlation analysis between clinical efficacy and biological factors (e.g., transcriptome data)^{14, 15, 16} is not suitable to identify appropriate biomarkers for patient stratification, as it may detect pseudo-correlations rather than the actual causal relationship. Instead, a quantitative model-based framework that describes AD pathogenesis is required to identify biomarkers for patient stratification and to evaluate the clinical efficacy of new hypothetical therapies such as the one that inhibits a combination of cytokines¹⁷.

As a quantitative approach to elucidate disease pathogenesis, quantitative systems pharmacology (QSP) has been successfully applied to enhance understanding of the pathogenesis of many inflammatory diseases in the context of translational drug development^{18, 19}. QSP uses mathematical models to describe a systems-level understanding of pathogenesis and drug effects by integrating biological and pharmacological knowledge²⁰. For example, the QSP approach has been applied to evaluate the efficacy of approved and experimental drugs in rheumatoid arthritis²¹, the effects of a hypothetical drug on cytokine behaviors in Crohn's disease²², and the relationship between Th1/Th2 responses and exposure levels of lipopolysaccharide in

asthma²³. QSP modeling can be leveraged with model-based meta-analysis, which integrates data from different clinical trials with current understanding on disease pathogenesis, to make maximal use of clinical efficacy data of multiple therapies with different MoA²⁴.

In this study, we develop a QSP model that describes the relationship between cytokines and AD pathogenesis using clinical efficacy data of nine approved or investigational biologic drugs: dupilumab, lebrikizumab, tralokinumab, secukinumab, fezakinumab, nemolizumab, tezepelumab, GBR 830, and recombinant interferon-gamma (rIFN γ). We use the model to reveal the pathophysiological backgrounds of dupilumab poor responders and to identify promising drug targets to treat the dupilumab poor responders.

2. METHODS

Our QSP model explicitly describes regulatory links between drugs, biological factors, and an efficacy endpoint using graphical scheme and ordinary differential equations (ODEs). The model development processes consist of 1) selecting drugs and biological factors to be described in the model, 2) formulating causal relationship between the biological factors using ODEs, 3) quantifying drug effects on the biological factors, and 4) tuning model parameters of the ODEs so that the model reproduce reference data, which were obtained from published clinical trials.

2.1. Selection of drugs and biological factors

We considered only the drugs that showed a higher (not necessarily statistically significant) efficacy than placebo in a placebo-controlled double-blinded clinical study

(Table 1, the process is detailed in Supplementary Information (SI) Section 1, Figure S1) and adopted only the highest dose of each drug. For example, we adopted the highest dose, 300 mg weekly, used in the Ph3 study for dupilumab. It allowed us to assess the maximal effects of the MoA and integrate the clinical data from different MoA, rather than investigating the relationship between pharmacokinetics and pharmacodynamics.

We did not consider small molecules because they can affect many cytokines, making it difficult to associate clinical efficacy with a specific cytokine in our model. For example, a Janus kinase (JAK) inhibitor, abrocitinib, was excluded in this study, as JAK inhibitors block signaling of a considerable number of cytokines and growth factors.

As biological factors, our model described skin barrier integrity and infiltrated pathogens, which were described as key factors in our previously published mathematical model of AD pathogenesis²⁶ as well as the cytokines and OX40L in the skin that have been specifically targeted by the drugs (TABLE 1). Our model also described their related subtypes of Th cells to explicitly represent feedforward and feedback mechanisms (e.g., Th2 secretes IL-4, which promotes T cell differentiation toward Th2).

Some biological factors such as dendritic cells and AMPs were not described as model variables but were taken into consideration as a rationale for regulatory processes in our model (e.g., IL-17A decreases infiltrated pathogens via increasing AMPs), to make the model simpler, yet interpretable. Our model excluded the targets of the excluded drugs because the contribution of those targets on AD pathogenesis has not been clinically confirmed (e.g., IgE was not considered because anti-IgE antibody omalizumab was excluded due to lack of efficacy in clinical trials).

The EASI score was adopted as a model variable to represent an efficacy endpoint.

2.2. Formulating causal relationship between biological factors

We developed a mathematical model consisting of 14 ODEs with 51 parameters to simulate the efficacy of the nine drugs (detailed in SI Section 3). The functional relationships between biological factors in the model were described according to published experimental evidence based on human data. We assumed that each cytokine independently affects skin barrier integrity and infiltrated pathogens (e.g., the level of IL-4 does not affect the influence of IL-13 on skin barrier integrity.) as cytokines have shown additive influence on filaggrin expression, which is related to skin barrier integrity and antimicrobial peptides (AMPs), which decrease microbial pathogens^{27, 28}.

The model was implemented in Python 3.7.6 (Python Software Foundation).

2.3. Modelling drug effects

All the drugs, except for rIFN γ , inhibit signaling from biological factors by blocking their binding to the receptors by targeting the cytokine itself or its receptor. Effective concentration of the target biological factor in the skin at time t , $c(t)$, was modelled by

$$c(t) = (1 - r_{\text{inhibit}})c^*(t), \quad (1)$$

where $c^*(t)$ is the actual concentration of the target biological factor in the skin at t and r_{inhibit} is the inhibition rate of the target biological factor in the drug treatment. The value of r_{inhibit} was determined using the published data on IC_{50} and the mean concentration of drugs in the skin²⁹ that was estimated from their concentration in the serum measured in clinical trials (detailed in SI Section 3.4 and TABLE S3). The estimated value of r_{inhibit} was

0.99 for all the antibodies, except for $r_{\text{inhibit}}=0.44$ for tralokinumab (detailed in SI section 3.4).

Administered rIFNg increases the effective amount of IFNg. Effective concentration of IFNg in the skin at t , $c_{\text{IFNg}}(t)$, is modelled by

$$c_{\text{IFNg}}(t) = c_{\text{IFNg}}^*(t) + c_{\text{rIFNg}}, \quad (2)$$

where $c_{\text{IFNg}}^*(t)$ is the actual concentration of IFNg in the skin at t and c_{rIFNg} is the mean concentration of rIFNg in the skin after rIFNg administration. c_{rIFNg} was estimated as 210 based on the pharmacokinetics data of rIFNg³⁰ (detailed in SI Section 3.4).

2.4. Modelling virtual patients and parameter tuning

We represented each virtual patient by a set of values for the 51 model parameters, where each parameter value is taken from log-normal distribution³¹ (TABLE S4). The probability distribution function, $f(k_n)$, for the n -th parameter, k_n , is defined by

$$f(k_n) = \frac{1}{\sqrt{2\pi}\sigma_n k_n} \exp\left(-\frac{(\ln k_n - \mu_n)^2}{2\sigma_n^2}\right), \quad (3)$$

where μ_n and σ_n are the distribution parameters that represent the mean and the standard deviation of $\ln k_n$, respectively.

We tuned 102 parameters (μ_n and σ_n) that define distributions of the 51 model

parameters(detailed in SI Section 4). The 11 parameters, μ_n for elimination rates of the 11 biological factors, were determined using the half-lives measured *in vivo* (serum) in humans (TABLE S5). The remaining 91 parameters were tuned so that the model reproduces the following clinical data;

- The mean and the coefficient of variation of levels of biological factors in observational studies (TABLE S2) and
- The mean EASI scores and EASI-75 when the nine drugs were applied in clinical trials (FIGURE 1).

We collected reference data for efficacy endpoints from published clinical trials of the selected drugs. We used EASI-75 (and its related %improved EASI and mean EASI score) as an efficacy endpoint that was adopted as one of the most common primary endpoints in Ph3 studies^{10,25}. EASI-75 was normalized to compare clinical efficacies of different clinical trials (detailed in SI Section 2).

Reference data for the levels of biological factors, including cytokines, OX40 ligand (OX40L), and T cells in AD skin lesions, were obtained from human skin biopsy data in published observational studies (TABLE S2). We described protein levels of cytokines and OX40L and count levels of T cells in AD lesion skin by fold change relative to those for healthy subjects or to non-lesional skin of the same AD patients. The skin barrier integrity and infiltrated pathogens were regarded as latent state variables, which have no reference data to be compared with simulated values.

Simulated data for the baseline levels of the biological factors were obtained by simulating steady-state levels of biological factors (at 1000 weeks without drug treatment) using a large number of virtual patients (1000 virtual patients) by randomly sampling each of the parameter values from the distribution in Eq.(3).

Simulated data for the mean EASI and the EASI-75 were obtained by simulating drug treatment for the same number of virtual patients as for the corresponding clinical trial (TABLE 1), while the simulated clinical trial was repeated 1000 times to calculate the 95% confidence interval (CI).

2.5. Identification of pathophysiological backgrounds that influence %improved EASI of each drug

To identify the pathophysiological backgrounds of virtual patients that influence %improved EASI of each drug most, we conducted a global sensitivity analysis of the model parameters with respect to %improved EASI. We produced 1000 virtual patients by varying the 51 parameters that represent their pathophysiological backgrounds using Latin hypercube sampling (LHS) and computed partial rank correlation coefficient (PRCC)³² between each parameter and %improved EASI of each drug. LHS is a sampling method to explore the entire space of multidimensional parameters efficiently, and PRCC represents a rank correlation coefficient that is controlled for confounding effects that could lead to detecting pseudo-correlations. The evaluated ranges of $\ln k_n$ were $[\mu_n - \sigma_n, \mu_n + \sigma_n]$. The p -values for the PRCC were adjusted for multiple testing with the Bonferroni procedure, where a significance level of adjusted $p < 0.05$ was used.

2.6. Simulation of clinical efficacy of hypothetical therapy for dupilumab poor responders

We simulated EASI-75 of a hypothetical therapy for virtual dupilumab poor responders. Virtual dupilumab poor responders were the virtual patients who did not achieve the criterion of EASI-75 (more than 75% improvement of EASI score from week 0) at 24

weeks after dosing dupilumab in 1000 virtual patients. The virtual poor responders were treated with a single drug, combinations of two drugs, and a hypothetical therapy that inhibited combinations of two cytokines or all the cytokines considered in the model (inhibiting IL-4, IL-13, IL-17A, IL-22, IL-31, IFN γ , and thymic stromal lymphopoietin: TSLP by 99%).

3. RESULTS

3.1. Normalization of EASI enabled comparison of clinical efficacy of nine drugs

We selected nine biologic drugs with different MoA that have shown clinical efficacy compared to placebo at least at the population average (TABLE 1) and compared the clinical efficacy of the drugs by mean EASI score, %improved EASI, and EASI-75 after normalization (FIGURE 1). Dupilumab and lebrikizumab showed the highest efficacy among the nine drugs, suggesting that their common target, IL-13, has the highest contribution on AD pathogenesis among the drug targets evaluated in this study. All other drugs also achieved a certain efficacy compared to placebo, confirming the clinical relevance of all the targets to AD pathogenesis.

3.2. QSP model reproduced clinical efficacy of nine drugs

We developed a QSP model (FIGURE 2) that describes the MoA for the nine biologic drugs, i.e., regulatory mechanisms between the biological factors and drugs using the published efficacy data from clinical trials.

Our model includes 15 biological factors that are targeted by the nine drugs or that are known to be related to AD pathogenesis (TABLES 2). They are seven cytokines (IL-4,

IL-13, IL-17A, IL-22, IL-31, IFN γ , and TSLP), OX40L, and four subsets of helper T cell (Th1, Th2, Th17, and Th22) that are the main source of the cytokines, except for TSLP which is secreted from keratinocytes. The model also includes “infiltrated pathogens” and “skin barrier integrity” as the main variables for a model of AD pathogenesis²⁶, and the EASI score as an efficacy endpoint of each virtual patient. The effects of the drugs were modelled by decreasing or increasing effective concentrations of their target cytokines or OX40L (TABLE S2).

The model contains 51 parameters (e.g., the recovery rate of skin barrier via skin turnover, k_1). We assumed the parameter values, corresponding to the strengths of the regulatory processes, vary between AD patients, so that virtual patients are defined by sets of 51 parameter values. We tuned the distributions of the 51 parameters (TABLE S4) to reproduce the mean and the coefficient of variation of the biological factors in observational studies and mean EASI score and EASI-75 of the drugs (FIGURE 3). The root mean square errors of the mean EASI and EASI-75 between the simulated and reference data were 2.1 (out of 72 = the max EASI) and 7.4%, respectively.

3.3. Global sensitivity analysis detected correlation between turnover rates of IL-13 in the skin and clinical efficacy of dupilumab

The variation in the responsiveness to each drug among the patients is considered to be due to the heterogeneity in the pathophysiological backgrounds of the patients. The responder rates could be improved by patient stratification based on biomarkers that reflect pathophysiological backgrounds³³. Using the QSP model, we can investigate which pathophysiological backgrounds have influence on clinical efficacy of each drug and which cytokines in the skin can be promising biomarkers for patient stratification. We

performed a global sensitivity analysis of the model to investigate the influence of the 51 model parameters (that represent pathophysiological backgrounds of the virtual patients) on %improve EASI of each drug using the LHS-PRCC (FIGURE 4).

Ten model parameters had a significant PRCC with the %improved EASI by dupilumab (FIGURE 4). Four out of the ten parameters are IL-13-related (k_{13} , k_{14} , b_2 , and d_{11}), and the remaining six parameters are skin barrier-related parameters (k_1 , k_3 , b_4 , b_6 , d_1 , and d_3) that correspond to placebo effects and baseline severity of skin barrier defects rather than each MoA (SI Section 5). The four IL-13-related parameters (k_{13} , k_{14} , b_2 , and d_{11}) can characterize responders for dupilumab, as virtual patients with higher k_{13} , k_{14} , and b_2 and a lower d_{11} were more responsive to treatment by dupilumab. The parameter, b_2 , describes the influence of IL-13 on skin barrier damage. IL-4-related parameters (k_{11} , k_{12} , b_1 , b_7 , and d_{10}) did not have a significant PRCC with %improved EASI by dupilumab, which inhibits both IL-4 and IL-13 signaling, in consistent with the report that clinical efficacy of dupilumab were not correlated with the baseline level of IL-4 mRNA expression¹⁴. We confirmed that the ten model parameters had different distributions for good and poor responders for dupilumab (SI Section 6).

As three out of the four IL-13 related parameters, k_{13} , k_{14} , and d_{11} , affect the IL-13 baseline level, we hypothesized that baseline levels of some cytokines in the skin could be used as predictive markers of good/poor responders for dupilumab and other drugs. To test this hypothesis, we stratified virtual patients based on their baseline cytokine levels for varying pre-defined threshold values. For the virtual patients whose baseline cytokine level is greater than the threshold value, we simulated the %improved EASI at week 24 of each drug (FIGURE 5). For dupilumab, EASI-75 was improved for patients with a higher IL-13 baseline level. It is consistent with the results from actual clinical trials of dupilumab, where

a higher efficacy was observed in the AD patients with higher baseline messenger RNA (mRNA) levels of IL-13¹⁴.

3.4. Simulated hypothetical therapies for dupilumab poor responders revealed simultaneous inhibition of IL-13 and IL-22 were effective whereas the nine biologic drugs were ineffective

The proportion of poor responders to dupilumab; the actual and simulated percentages of patients who did not achieve EASI-75 at 24 weeks, was 31%¹⁰ and 35% [95%CI 30.0%-41.9%] respectively (FIGURE 3). However, therapeutic options for the dupilumab poor responders are limited to increasing topical corticosteroids and adding systemic immunosuppressive agents, although the dupilumab poor responders are often resistant to these treatments and require monitoring for adverse effects³⁴.

We hypothesized that the dupilumab poor responders could be responsive to other targeted biologic drugs with different MoA, considering the heterogeneity of AD pathogenesis, and evaluated the potential efficacy of all nine drugs (FIGURE 6a). Every one of the nine drugs failed to show clinical responses in virtual dupilumab poor responders where maximal calculated responder rates, based on EASI-75 at 24 weeks, were only 1.9% [95%CI 0.6%-3.4%] in fezakinumab. These low efficacies imply an upper efficacy ceiling for drugs that target single cytokines to treat dupilumab poor responders.

We then evaluated the potential efficacy of hypothetical therapies that inhibit two cytokines, mimicking a bispecific antibody, for the virtual dupilumab poor responders. Our simulation demonstrated that dosing one additional drug to dupilumab achieved a better efficacy for virtual dupilumab poor responders (FIGURE 6b). The maximal EASI-75 in the virtual dupilumab poor responders (0% achieving EASI-75 at 24 weeks with dupilumab

therapy) at 24 weeks was 23.0% [95%CI 18.4%-27.3%] in dupilumab + fezakinumab, implying that inhibition of both IL-13 and IL-22 would be a promising combination for treatment of dupilumab poor responders. Indeed, inhibition of both IL-13 and IL-22 showed the highest clinical responses among all the combinations of two cytokines (FIGURE 6c), with EASI-75 at 24 weeks being 21.6% [95%CI 17.4%-25.5%]. These results are in concordance with a clinically observed negative correlation between the clinical efficacy of dupilumab and the baseline level of IL-22 mRNA expression (not significant, rank correlation coefficient -0.208 with p -value of 0.422)¹⁴. The simulation results, in combination with the clinical observation¹⁴, suggest that inhibition of IL-22 in addition to the dupilumab treatment is effective for dupilumab poor responders.

We also confirmed that blocking all targeted cytokines (inhibiting IL-4, IL-13, IL-17A, IL-22, IL-31, IFN γ , and TSLP by 99%) achieved a higher EASI-75 (33.8% [95%CI 28.8%-38.7%], FIGURE 6c). The responder rate did not reach 100% even when all the cytokines were blocked because some cytokines have not only detrimental but also beneficial effects. For example, IL-17A and IL-22 damage the skin barrier by inhibiting epidermal differentiation (detrimental effects) while they decrease infiltrated pathogens via increasing AMP (beneficial effects). Hence, inhibition of cytokines can partly exacerbate the AD symptoms, suggesting that finding optimal combinations of drugs requires a systems-level investigation.

4. DISCUSSION

4.1. QSP model to simulate biologics efficacy

Several biologic drugs targeting AD pathogenic cytokines have been developed and shown clinical efficacy to some extent in AD patients. Although only one biologic drug,

dupilumab, has been currently approved, it is useful to conduct model-based meta-analysis by integrating the results from clinical trials of other biologic drugs, including those that failed to show clinically significant efficacy and those under development, to enhance the understanding of AD pathogenesis and clinical efficacy of drugs with different MoA. In this study, we conducted model-based meta-analysis of clinical trials on the nine biologic drugs for AD (dupilumab, lebrikizumab, tralokinumab, secukinumab, fezakinumab, nemolizumab, and tezepelumab, GBR830, and rIFN γ) that were published by Dec 2020 (FIGURE S1), and developed a QSP model of biologics efficacy in AD patients (FIGURE 2). This QSP model describes dynamic relationships between biological factors and clinical efficacies by integrating knowledge obtained from experiments using human samples and clinical trials of multiple drugs. The model reproduced the clinical efficacies of the biologic drugs observed in clinical trials and baseline levels of biological factors (e.g., cytokines) in the skin from published studies (FIGURE 3).

4.2. Comparison of clinical efficacies of biologics

Comparison of clinical efficacies (FIGURE 1) demonstrated that dupilumab and lebrikizumab showed the highest efficacy among the nine drugs investigated in this study, suggesting that their common target, IL-13, is the most crucial target to improve AD severity scores. The comparable efficacy between dupilumab (inhibiting both IL-4 and IL-13) and lebrikizumab (inhibiting IL-13 only) may suggest inhibition of IL-4 signaling has a minor contribution on the efficacy of dupilumab. Another anti-IL-13 antibody, tralokinumab, showed a significantly lower clinical efficacy than lebrikizumab. Lebrikizumab inhibits binding of IL-13 to IL-13R α 1 only, while tralokinumab inhibits binding to both IL-13R α 1 and IL-13R α 2. IL-13R α 1 forms a heterodimeric receptor with IL-4R α and

is related to the effects of IL-13 signaling in AD pathogenesis while IL-13R α 2 is a decoy receptor to decrease IL-13 signaling via IL-13R α 1. Hence, tralokinumab not only inhibits IL-13 signaling via IL-13R α 1 but also enhances IL-13 signaling via inhibition of IL-13 binding to IL-13R α 2³⁵. In our simulation, effective inhibition of IL-13 signaling by tralokinumab was estimated 44% of lebrikizumab ($e_{a2} = 0.44$). The difference in the efficacy between lebrikizumab and tralokinumab may come from different mechanisms for IL-13 inhibition, dosing regimens, or trial design.

4.3. Pathophysiological backgrounds of dupilumab poor responders

This study presents a QSP-based approach to identify potential predictive biomarkers of clinical efficacy through mechanistic model-based simulation. We used the developed model to explore pathophysiological backgrounds of dupilumab poor responders. Our simulation demonstrated that the higher responder rates for dupilumab are expected in patients with the higher baseline level of IL-13 in the skin (FIGURES 4 and 5). Although it also showed baseline levels of other cytokines (e.g., IFN γ) in the skin influence responder rates, these influences may be due to a pseudo-correlation of the cytokines with clinical efficacy because the parameters related to those cytokines were not detected as important in the global sensitivity analysis, which evaluates the “causative” influence of the parameters on efficacy. The cytokines detected due to the pseudo-correlation should not be used as predictive biomarkers for patient stratification, because such pseudo-correlations may have low reproducibility. Hence, our simulations suggest that the baseline level of IL-13 in the skin would be more suitable than other cytokines to be used as a biomarker for patient stratification in dupilumab treatment.

4.4. Simulated efficacy of hypothetical therapy in dupilumab poor responders

We also used the model to investigate alternative therapeutic options for virtual dupilumab poor responders. Our simulation results suggested inhibition of a single cytokine would be insufficient to achieve clinical response in virtual dupilumab poor responders, whereas inhibition of multiple cytokines could achieve clinical response (FIGURE 6a,b). Especially, IL-13 and IL-22 were identified to be the best combination to treat virtual dupilumab poor responders (FIGURE 6c). Inhibition of two cytokines can be realized by a bispecific antibody as well as combination of two antibodies.

Our simulated hypothetical therapy that inhibits all the cytokines in this model (IL-4, IL-13, IL-17A, IL-22, IL-31, IFN γ , and TSLP) showed higher clinical efficacy than inhibiting single and a combination of two cytokines (FIGURE 6c). These results suggest that inhibiting multiple cytokines can exert higher efficacy than biologic drugs targeting only one or two cytokines. In fact, the approach to inhibit signaling of multiple cytokines has been already realized by JAK inhibitors. For instance, abrocitinib blocks JAK1, which is an intracellular tyrosine kinase linked to intracellular domains of many cytokine receptors, including IL-4, IL-13, IL-22, IL-31, IFN γ , and TSLP. Abrocitinib showed comparable efficacy with dupilumab¹¹, but there were still a significant percentage of poor responders. One of the reasons why even multiple cytokine inhibition cannot achieve clinical response in all AD patients is that inhibition of cytokines can deteriorate AD symptoms because some cytokines have both detrimental and beneficial effects in AD pathogenesis and the contributions of each cytokine on AD pathogenesis would vary among the AD patients. Hence, appropriate drugs would vary according to the pathophysiological backgrounds of the patients. Patient stratification may be beneficial not only for biologic drugs but also for the drugs that target multiple cytokines.

4.5. Limitation of this study using the model

We used clinical efficacy results of the biologic drugs as the reference data to tune the model parameters. We adopted Ph2 as well as Ph3 studies to make a maximal use of available clinical data (TABLE 1). However, the results from Ph2 studies with a rather small number of patients need to be confirmed with those from Ph3 studies with a larger number of patients. Our model assumptions include that virtual patients were generated from single modal distributions of the model parameters. There could be a multimodal distribution due to the genetic backgrounds or other demographic variances in a real population of AD patients. For the practical purposes of generating this model we assumed the %improved EASI was comparable across clinical trials. We know that outcome measures may be influenced by the concomitant use of topical corticosteroids and the statistical methods used to adjust for or censor topical corticosteroid use and to impute missing data. The model will need to be updated according to availability of the reference data and assumptions if these are changed as new data emerge.

4.6. Prospects for model-informed drug development

The proposed model could be further expanded for future development of new drugs for AD, by including new drug targets and pharmacokinetics and pharmacodynamics profiles of new drugs. The expanded model will be a useful tool to computationally evaluate potential clinical efficacies of new drug candidates, to identify biomarkers for patient stratification, to clarify the difference from existing drugs (e.g., showing significant efficacy in dupilumab poor responders), and to design optimal doses with considering variations in pathophysiological backgrounds.

Such simulated data may inform design of future clinical trials. For example, simulated variability in drug efficacy may help determine the number of participants and the study periods required, comparison of the simulated efficacy for new drug candidates and competitive drugs may predict the probability of success in achieving clinical efficacy, and simulated patient stratification may determine pathophysiological backgrounds of patients to be recruited. The model simulation may also enhance understanding of clinical trial results. For example, sensitivity analysis of the model may identify pathophysiological backgrounds that affect the individual variability in pharmacokinetics and clinical efficacy (e.g., this study identified IL-13-related parameters to be related with the dupilumab efficacy). Furthermore, it could inform novel therapeutic approaches as a reverse translational research (e.g., simultaneous inhibition of IL-13 and IL-22 proposed in this study).

The model contributes to a systems-level understanding of AD pathogenesis and the drug effects and to evaluate the effects of new potential drug targets by computational simulation. This could serve as model-informed drug development³⁶ for precision medicine. The code of the QSP model is available at https://github.com/Tanaka-Group/AD_QSP_model.

TABLE 1 Drugs considered in this study

Drugs	Targets	Dose regimen (highest dose)	Available endpoints	efficacy	#patients in placebo/drug arm (Phase)
Dupilumab ¹⁰ (anti-IL-4 receptor subunit α antibody)	IL-4 and IL-13	300 mg qw, s.c. +TCS	EASI-75, %improved EASI %improved SCORAD		264/270(Ph3)
Lebrikizumab ⁴² (anti-IL-13 antibody)	IL-13	250 mg q2w, s.c. +TCS	EASI-75, %improved EASI		52/75 (Ph2)
Tralokinumab ⁴¹ (anti-IL-13 antibody)	IL-13	300 mg q2w, s.c. +TCS	EASI-75 %improved EASI		126/252(Ph3)
Secukinumab ¹⁶ (anti-IL-17A antibody)	IL-17A	300 mg qw for 4 weeks, followed by 300 mg q4w	%improved EASI %improved SCORAD		14/27 (Ph2)
Fezakinumab ³⁸ (anti-IL-22 antibody)	IL-22	600 mg at day 0, followed by 300 mg q2w, i.v.	%improved SCORAD [†]		20/40 (Ph2)
Nemolizumab ³⁷ (anti-IL-31 receptor subunit α antibody)	IL-31	60 mg q4w, s.c.	EASI-75, %improved EASI		72/143 (Ph3)
Tezepelumab ³⁹ (anti-TSLP antibody)	TSLP	280 mg q2w, s.c. +TCS	EASI-75, %improved EASI %improved SCORAD		56/55 (Ph2)

GBR 830 ⁴⁰ (anti-OX40L antibody)	OX40L	10 mg/kg q4w, i.v.	%improved EASI	16/46 (Ph2)
rIFNg ⁴³	IFNg	50 ug/m2 qd, s.c. +TCS	% improved AD scores [‡]	43/40 (Ph2)

†: %improved EASI was estimated from %improved SCORAD using a regression curve (FIGURE S2), ‡: the mean value of the %improved AD scores were regarded as %improved EASI because the evaluated signs were same as those for EASI (erythema, induration, excoriations, and lichenification). When there were multiple clinical studies per drug, we adopted the clinical study of combination therapy with topical corticosteroids, which is more reflective of the likely clinical use compared with monotherapy, and studies with the largest number of patients.

Abbreviations:qw, every week; q2w, every 2 weeks; q4w, every 4 weeks;qd, every day;s.c., subcutaneous administration;i.v., intravenous administration; +TCS, concomitant use of topical corticosteroids.

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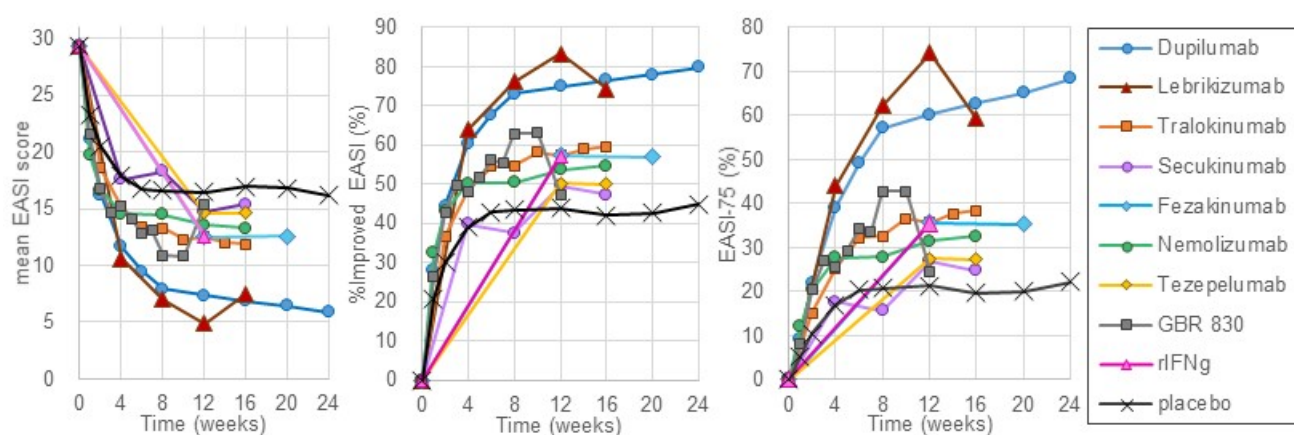


FIGURE 1Reference data collected from published clinical trials. The mean EASI score, %improved EASI, and EASI-75 of nine drugs (dupilumab, lebrikizumab, tralokinumab, GBR 830, fezakinumab, rIFNg, tezepelumab, nemolizumab, secukinumab) were normalized according to the method detailed in SI Section 2.

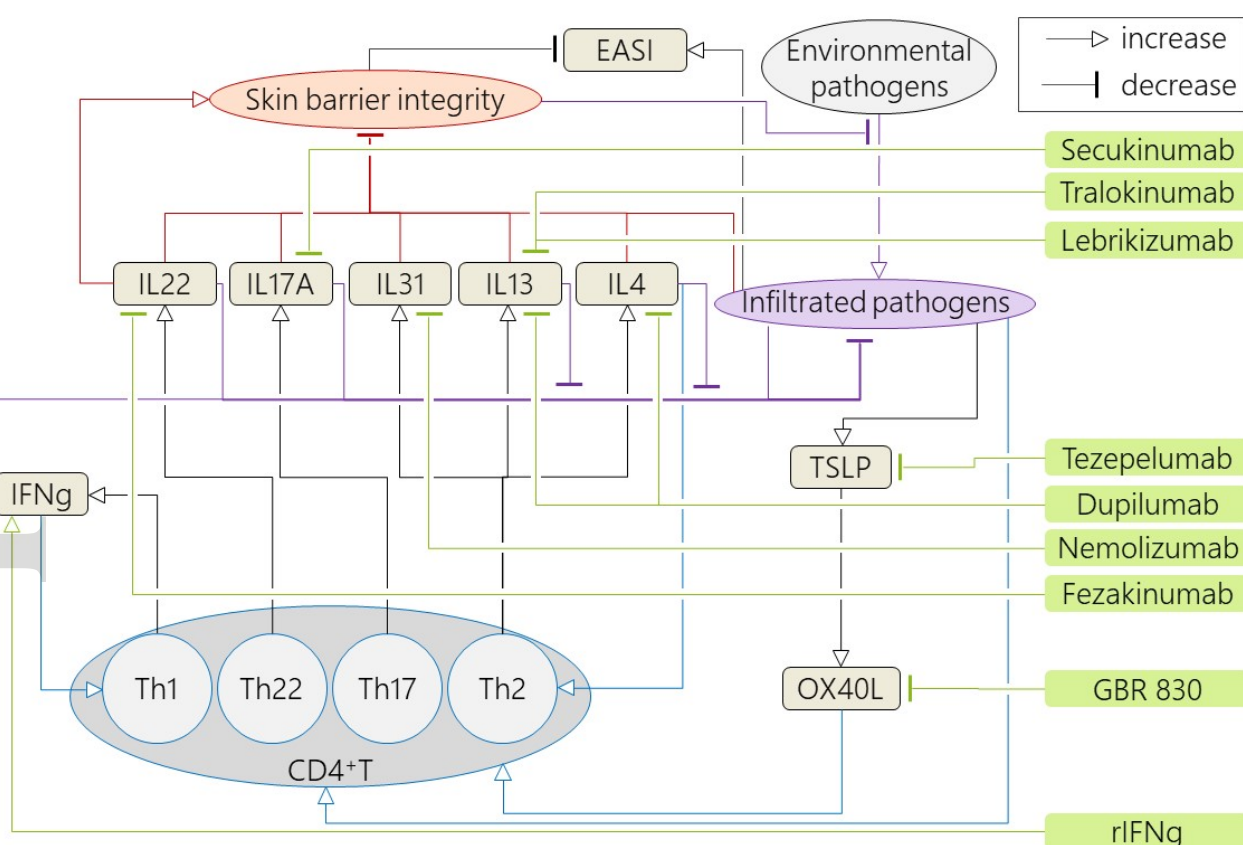


FIGURE 2Overview of the proposed mathematical model. The model comprises of an efficacy endpoint (EASI score), biological factors (skin barrier integrity, infiltrated pathogens,

cytokines, T cells) and drugs (dupilumab, lebrikizumab, tralokinumab, GBR 830, fezakinumab, rIFN γ , tezepelumab, nemolizumab, secukinumab). The functional relationships between biological factors were described according to published human data (details in SI Section 3).

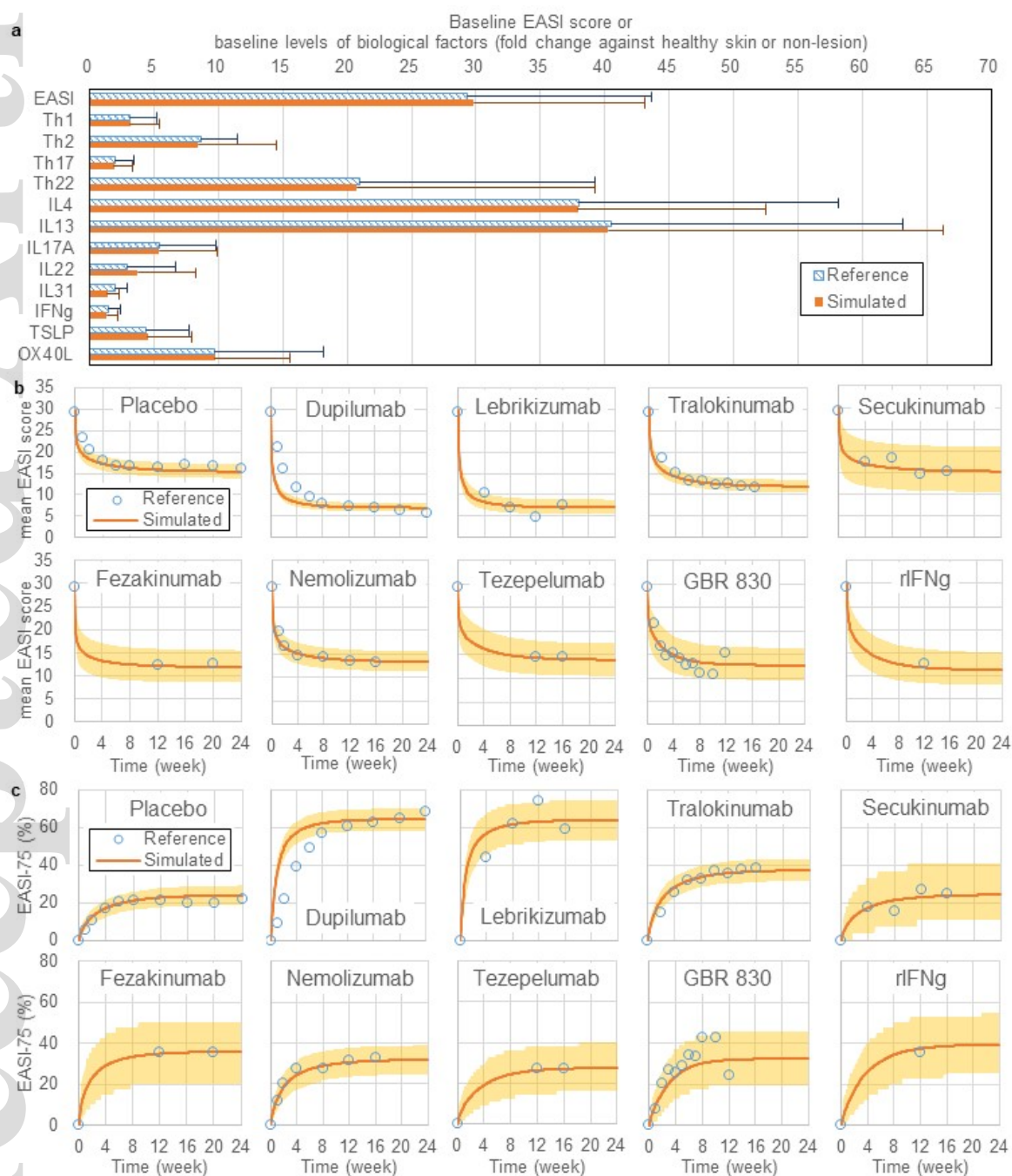


FIGURE 3 Simulated and reference data of (a) baseline levels of biological factors,

(b) mean EASI score, and (c) EASI-75. The model parameters were tuned to minimize the difference between simulated and reference data (detailed in SI section 4.2). (a) Reference data (striped bars) are the measured values of the biological factors in observational studies. Simulated data (filled bars) were obtained by simulating steady-state levels of biological factors (at 1000 weeks without drug treatment) using 1000 virtual patients. Error bars are standard deviations. (b and c) Reference data (unfilled circles) are mean EASI scores (b) and EASI-75 (c) after treatment of each drug. Simulated data for the mean EASI and the EASI-75 were obtained by simulating the efficacies of drug treatment using the same number of virtual patients as for the clinical trials (TABLE 1), and the simulated clinical trial was repeated 1000 times to calculate 95% CI (lines: mean, shaded area: 95% CI).

Parameters		%improved EASI at week 24									
		Placebo	Dupilumab	Lebrikizumab	Tralokinumab	Secukinumab	Fezakinumab	Nemolizumab	Tezepelumab	GBR 830	rIFNg
Recovery rate of skin barrier integrity via skin turnover	k1	-0.5	-0.6	-0.6	-0.5	-0.5	-0.6	-0.5	-0.5	-0.5	-0.6
Recovery rate of skin barrier integrity via IL-22	k2	0.7	0.6	0.6	0.7	0.7	0.7	0.7	0.7	0.7	0.7
Recovery rate of skin barrier integrity via placebo effects	k3	0.7	0.6	0.6	0.7	0.7	0.7	0.7	0.7	0.7	0.7
Rate of pathogen infiltration	k4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Rate of differentiation of naïve T cells to Th1	k5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Rate of differentiation of naïve T cells to Th2	k6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Rate of differentiation of naïve T cells to Th17	k7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Rate of differentiation of naïve T cells to Th22	k8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Strength of polarization for Th1 differentiation	k9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.2
Strength of polarization for Th2 differentiation	k10	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
IL-4 secretion rate via Th2	k11	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
IL-4 secretion rate via other pathways	k12	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
IL-13 secretion rate via Th2	k13	0.0	0.2	0.2	0.1	0.0	0.1	0.1	0.1	0.1	0.1
IL-13 secretion rate via other pathways	k14	0.1	0.3	0.3	0.0	0.1	0.0	0.0	0.0	0.0	0.0
IL-17A secretion rate via Th17	k15	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
IL-17A secretion rate via other factors	k16	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
IL-22 secretion rate via Th22	k17	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
IL-22 secretion rate via other factors	k18	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
IL-31 secretion rate via Th2	k19	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
IL-31 secretion rate via other factors	k20	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
IFNg secretion rate via Th1	k21	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
IFNg secretion rate via other factors	k22	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
TSLP secretion rate via infiltrated pathogens	k23	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
TSLP secretion rate via other factors	k24	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
OX40L expression rates via TSLP	k25	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
OX40L expression rates via other factors	k26	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Inhibitory strength for recovery of skin barrier via IL-4	b1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Inhibitory strength for recovery of skin barrier via IL-13	b2	0.0	0.6	0.6	0.3	0.1	0.2	0.1	0.1	0.1	0.2
Inhibitory strength for recovery of skin barrier via IL-17	b3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Inhibitory strength for recovery of skin barrier via IL-22	b4	0.0	0.2	0.2	0.1	0.1	0.3	0.1	0.1	0.1	0.2
Inhibitory strength for recovery of skin barrier via IL-31	b5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
inhibitory strength for pathogens infiltration via skin barrier	b6	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Inhibitory strength for elimination of infiltrated pathogens via IL-4	b7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Inhibitory strength for elimination of infiltrated pathogens via IL-13	b8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Inhibitory strength for T cells elimination by OX40L	b9	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Degradation rate of skin barrier via skin turnover	d1	0.0	0.3	0.3	0.1	0.0	0.3	0.0	0.1	0.1	0.2
Degradation rate of skin barrier via IL-31	d2	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Degradation rate of skin barrier via infiltrated pathogens	d3	0.0	0.3	0.3	0.1	0.0	0.2	0.0	0.1	0.1	0.2
Elimination rate of infiltrated pathogens via infiltrated pathogens themselves	d4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Elimination rate of infiltrated pathogens via IL-17A	d5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Elimination rate of infiltrated pathogens via IL-22	d6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Elimination rate of infiltrated pathogens via IFNg	d7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Elimination rate of infiltrated pathogens via skin turnover	d8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
T cell elimination rate	d9	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Elimination rates for IL-4	d10	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Elimination rates for IL-13	d11	0.1	-0.2	-0.2	0.1	0.0	0.1	0.1	0.1	0.1	0.1
Elimination rates for IL-17A	d12	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Elimination rates for IL-22	d13	0.0	0.0	0.0	0.0	0.0	-0.2	0.0	0.0	0.0	0.1
Elimination rates for IL-31	d14	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Elimination rates for IFNg	d15	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Elimination rates for TSLP	d16	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Elimination rates for OX40L	d17	0.1	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0

FIGURE4Partial rank correlation coefficient (PRCC)between model parameters and%improved EASI by eachdrug treatment. 1000 virtual patients (1000 sets of 52 model parameter values) were generated by sampling 52 parameter values independently according to Latin hypercube sampling, and were treated by each drug to simulate %improved EASI at 24 weeks. Open

and crossed cells are statistically significant and not significant PRCC (absolute value >0.1 with adjusted p -values <0.05), respectively. Positive PRCC means that virtual patients with a higher value of the parameter achieve a higher %improve EASI by the drug treatment (e.g., k_3). Negative PRCC means that virtual patients with a lower value of the parameter achieve a higher %improve EASI by the drug treatment (e.g., k_1).

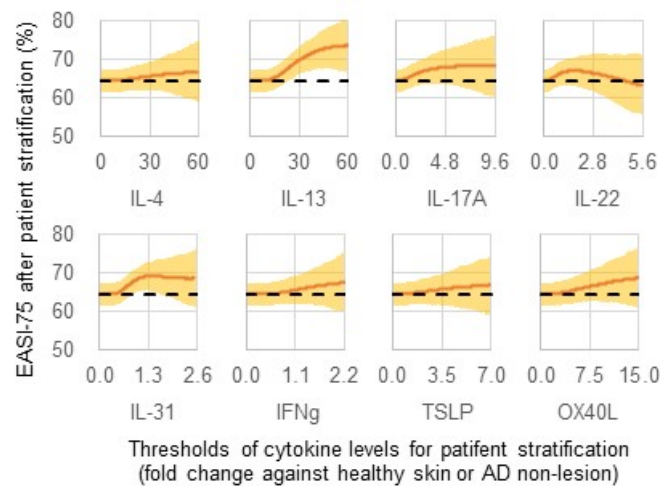


FIGURE 5 Simulated EASI-75 in dupilumab treatment after patient stratification with different thresholds of cytokine baseline levels. 1000 virtual patients (1000 sets of 52 model parameter values) were generated by randomly sampling each of the parameter values from the distribution in Eq.(3), and were stratified into those whose cytokine baseline level (before dupilumab treatment) was greater than the threshold (x-axis). EASI-75 at 24 weeks (y-axis) were calculated for the stratified patients. The number of stratified virtual patients decreases with an increasing threshold, while the threshold of zero includes all the virtual patients. The maximal threshold for each cytokine was set to ensure that at least 10% of the generated 1000 virtual patients are stratified. Orange solid lines and shaded areas are the mean value and 95% CI of 1000 simulations, respectively. Higher EASI-75 achieved with patient stratification (compared to without stratification with the threshold zero: dashed line) suggests a success in stratifying good responders.

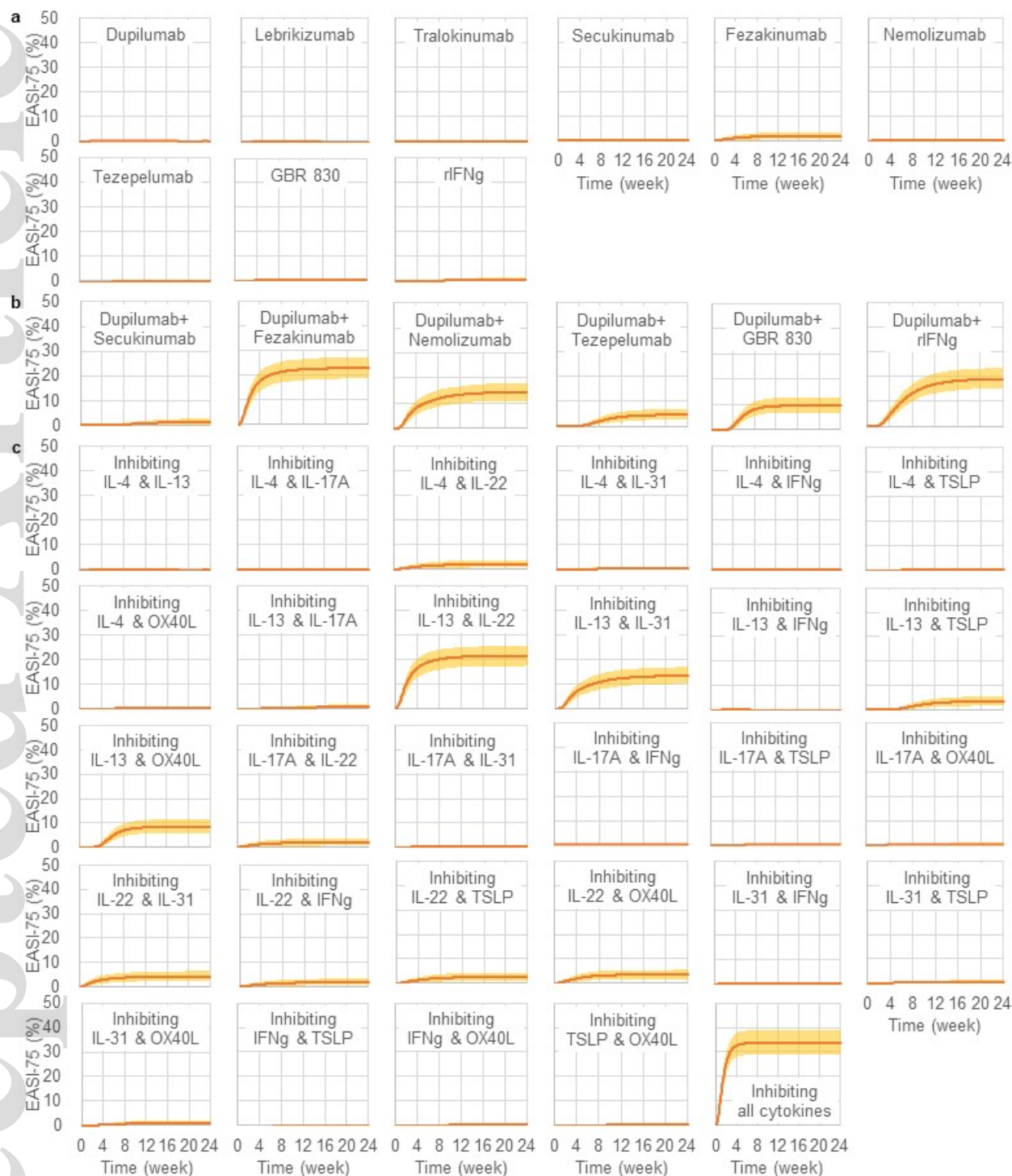


FIGURE 6 Simulated EASI-75 in virtual dupilumab poorresponders. The virtual dupilumab poor responders were treated in simulated clinical trials with (a) a single drug, (b) a combination of two drugs, and (c) blocking a combination of two cytokines or all the cytokines (inhibiting IL-4, IL-13, IL-17A, IL-22, IL-31, IFN γ , and TSLP by 99%). Virtual dupilumab poor

responders were the virtual patients who did not achieve the EASI-75 criterion at 24 weeks among 1000 virtual patients (mean 356 with 95% CI 300-419 virtual patients). The simulated clinical trial was repeated 1000 times to obtain 95% CI. Lines and shaded areas are the mean values and 95% CI of 1000 simulations, respectively.

Supplementary Information

A mathematical model to identify optimal combinations of drug targets for dupilumab poor responders in atopic dermatitis

Takuya Miyano, Alan D Irvine and Reiko J Tanaka

1. Selection of clinical studies

We selected clinical studies to be referenced in the QSP model according to pre-defined inclusion and exclusion criteria (FIGURE S1).

We searched the clinical trials that evaluated efficacy of biologic drugs in AD patients, where Ph2 studies were not searched if Ph3 results were available and case reports were not searched if placebo-controlled double-blind clinical trial data were available. We excluded investigational drugs if the clinical efficacies were not evaluated by a placebo-controlled study, if they failed to show a clinical efficacy compared to placebo, if the clinical trials recruited only a small number (<10) of AD patients, if evaluation periods were short (less than 4 weeks), or if data of efficacy endpoints were not published (TABLE S1). When there remained multiple clinical studies per drug, we adopted the clinical study of combination therapy with topical corticosteroids, which is more reflective of the likely clinical use compared with monotherapy, and studies with the largest number of patients.

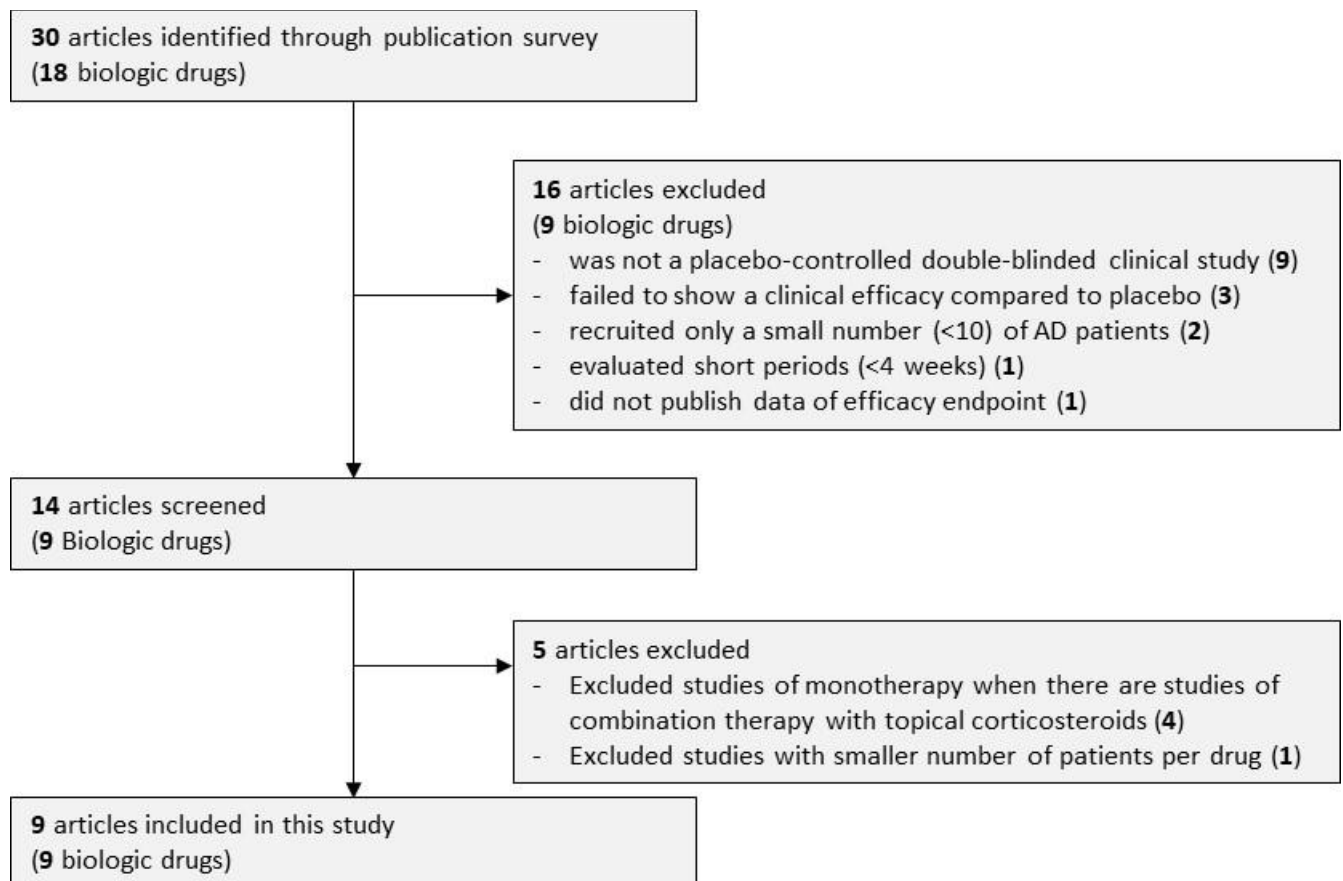


FIGURE S1 Clinical studies selection process

TABLE S1 Drugs excluded in this study

Drugs	Targets	#patients in placebo/drug arm (Phase)	Reasons to be excluded
Omalizumab ^{1, 2} (anti-IgE antibody)	IgE	4/4 and 7/13 (Ph4)	- It is difficult to interpret the results due to the small number of patients - Omalizumab showed comparable or lower clinical efficacy than placebo in terms of IGA score and %improved SCORAD (not significant)
Mepolizumab (anti-IL5 antibody)	IL-5	16/18 at baseline 11/11 at week 12 8/6 at week 16 4/4 at week 20 (Ph2) ³ 23/20 (Ph2) ⁴	- It is difficult to interpret the results due to the small number of patients after 12 weeks³ - Evaluation periods were short (2 weeks)⁴
MOR106 ⁵ (anti-IL-17C antibody)	IL-17C	N/A (Ph2)	- Data of the primary endpoint are unavailable - The interim analysis detected a low probability to meet the primary endpoint (%improve EASI)
Etokimab ⁶ (anti-IL-33 antibody)	IL-33	60/59-61 (Ph2)	Etokimab showed a lower clinical efficacy than placebo in terms of %improve EASI at several dose regimens including the highest dose (not significant)
Tocilizumab ⁷ (anti-IL-6 antibody)	IL-6	-/3	- Placebo-controlled double-blind clinical trial data are unavailable. - A single-arm trial of three AD patients showed tocilizumab significantly improved the EASI score compared with baseline but it is difficult to interpret the results due to the small number of patients
Ustekinumab (anti-IL-12/23 antibody)	IL-12 and IL-23	27/24-28 (Ph2) ⁸ 16/16 (Ph2) ⁹	Ustekinumab showed only comparable clinical efficacy to placebo in terms of %improve EASI (placebo: 37.5% vs. Ustekinumab: 38.2%-39.8% at week 12, not significant) ⁸ and SCORAD (less decreased in ustekinumab compared with placebo on average, not significant) ⁹
Infliximab (anti-TNFα antibody)	TNFα	-/9 ¹⁰ , 1 ¹¹	Placebo-controlled double-blind clinical trial data are unavailable (A single-arm trial of nine AD patients showed infliximab significantly improved the EASI score compared with baseline)
Etanercept	TNFα	-/2 ¹² , 2 ¹³	Placebo-controlled double-blind clinical trial data are unavailable
Rituximab (anti-CD20 antibody)	B cells	-/6 ¹⁴ , 2 ¹⁵ , 3 ¹⁶	Placebo-controlled double-blind clinical trial data are unavailable (A single-arm trial of six AD patients showed rituximab significantly improved the EASI score compared with baseline)

2. Data processing

2.1. Conversion of reported efficacy endpoints to %improved EASI

All the drugs, except for fezakinumab and rIFNg, reported %improved EASI as an efficacy endpoint.

For fezakinumab, we estimated %improved EASI from %improved SCORAD using a regression curve obtained from the relationship between %improved EASI and %improved SCORAD in clinical trials of multiple drugs^{1, 17, 18, 19} (FIGURE S2).

For rIFNg, we substituted %improved EASI by the mean value of the %improved scores of the disease signs evaluated (erythema, induration, excoriations, and lichenification)²⁰.

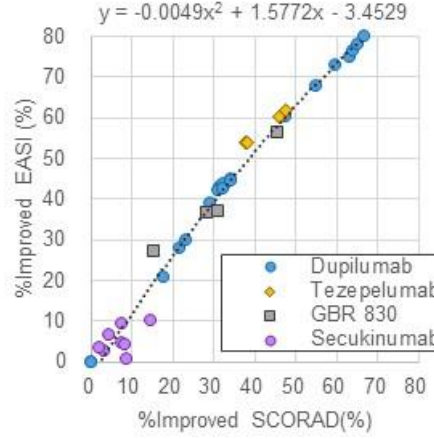


FIGURE S2 Regression curve to estimate %improved EASI from %improved SCORAD

2.2. Normalization of %improved EASI

%improved EASI was normalized to compare clinical efficacies evaluated in different clinical trials. We assumed that the observed %improved EASI is a sum of %improved EASI from net effects of each drug and that from placebo effects, and described normalized %improved EASI, $e_i(t)$, for the i -th drug at time t by

$$e_i(t) = (e_i^*(t) - e_{p_i}^*(t)) + e_{p_d}^*(t). \quad (S1)$$

The first term corresponds to the difference of the efficacy (%improved EASI) between drug ($e_i^*(t)$) and placebo groups ($e_{p_i}^*(t)$) to adjust for the different extent of the efficacy in the placebo group in each clinical study due to differences in patient background, concomitant drugs, and sites of study²¹. We then added the same extent of the efficacy in the placebo group ($e_{p_d}^*(t)$ in the dupilumab clinical trial) in this virtual simulation so that the normalized %improved EASI represents the scale of the observed %improved EASI (the sum of %improved EASI from net effects of each drug and that from placebo effects).

2.3. Normalization of mean EASI score

Normalized mean EASI score was calculated using the baseline mean EASI score (the mean EASI score before the trial) in dupilumab clinical trial¹ and the normalized %improved EASI as follows:

$$a_i(t) = \frac{a_d(0)(100 - e_i(t))}{100} \quad (S2)$$

where $a_i(t)$ is the normalized mean EASI score of i -th drug at t , $a_d(0)$ is the reported baseline mean EASI score in the dupilumab clinical trial (the mean value of placebo- and dupilumab-treated groups).

2.4. Normalization of EASI-75 using %improved EASI

Normalized EASI-75 was estimated from the normalized %improved EASI using a regression curve obtained from the relationship between %improved EASI and EASI-75 in clinical trials of multiple drugs^{1, 22, 18, 19, 23} (FIGURE S3). The relationship between %improved EASI and EASI-75 is affected by the variation of %improved EASI among the patients. Relatively large deviation of Tezepelumab and GBR 830 in the relationship may derive from the smaller variation between the patients due to the small number of patients in the Ph2 studies compared with the Ph3 studies (dupilumab, nemolizumab, and tralokinumab).

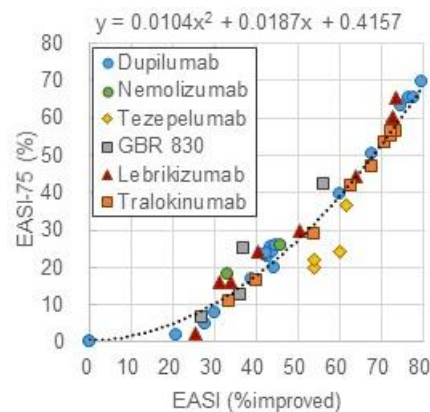


FIGURE S3 Regression curve to estimate EASI-75 from %improved EASI

3. Model structure

The model (FIGURE 2) is formulated by Eqs. (S3)-(S17) shown below. This section details components of the model: EASI score (the output of the model), skin barrier integrity and infiltrated pathogens, cytokines, T cells and drug effects (TABLE S2).

In this model, t is the time after the start of drug treatment. The baseline levels of biological factors ($t=0$) were obtained from the simulated steady-state level (after 1000 weeks) without any intervention. We referred to the reported levels of biological factors in observational studies as the reference values for the baseline levels, assuming that levels of the biological factors were stable before the start of drug treatments. We described protein levels of cytokines and OX40L and count levels of T cells in AD lesion skin by fold changes relative to those for healthy subjects or to non-lesional skin of the same AD patients in order to cancel out the effects of difference measurement methods and units used in different studies, and to avoid using an ambiguous unit of 'T cell count/field of view' in the immunohistochemistry.

TABLE S2 Biological factors as model variables

Factors	Model variables	Reason for inclusion	Reported levels in AD lesion	
			Mean (%CV)	Units
IL-4	$c_4(t)$	Target of dupilumab	38.0 (53) ^{24 a,d}	Fold change against healthy skin
IL-13	$c_{13}(t)$	Target of dupilumab, tralokinumab, and lebrikizumab	40.5 (56) ^{24 a,d}	Fold change against healthy skin
IL-17A	$c_{17}(t)$	Target of secukinumab	5.4 (81) ^{24 a,d}	Fold change against healthy skin
IL-22	$c_{22}(t)$	Target of fezakinumab	3.0 (124) ^{25 e,d}	Fold change against healthy skin
IL-31	$c_{31}(t)$	Target of nemolizumab	2.0 (49) ^{25 b,d}	Fold change against healthy skin
IFN γ	$c_9(t)$	Target of rIFN γ	1.5 (62) ^{24 a,d}	Fold change against healthy skin
TSLP	$c_{TS}(t)$	Target of tezepelumab	4.4 (76) ^{26 c}	Fold change against healthy skin
OX40L	$c_{OX}(t)$	Target of GBR 830	9.7 (87) ^{27 b}	Fold change against AD non-lesion
Th1 cells	$c_{11}(t)$	Main source of IFN γ	3.1 (68) ^{28, 29 b}	Fold change against AD non-lesion
Th2 cells	$c_{12}(t)$	Main source of IL-4, IL-13, and IL-31	8.7 (32) ^{28, 29 b}	Fold change against AD non-lesion
Th17 cells	$c_{17}(t)$	Main source of IL-17A	2.0 (76) ^{28, 29 b}	Fold change against AD non-lesion
Th22 cells	$c_{22}(t)$	Main source of IL-22	21.0 (87) ^{28, 29 b}	Fold change against AD non-lesion
Infiltrated pathogen	$p(t)$	Key factor in the previous model Its amount is affected by cytokines via AMP	- ^e	-
Skin barrier integrity	$s(t)$	Key factor in the previous model It protects skin from infiltrating pathogens It is related to severity of AD lesion	- ^e	-
EASI score	$e(t)$	Clinical endpoints	29.3 (49) ^{1 b,d,f}	-

a: mild-to-moderate AD patients. b: moderate-to-severe AD patients. c: both mild-to-moderate and moderate-to-severe AD patients. d: %CV was estimated from IQR. e: no reference data to be compared with simulated values. f: mean baseline value of dupilumab treatment: 29.0 and placebo treatment: 29.6 of AD patients in dupilumab clinical trial

3.1. EASI score, skin barrier integrity, and infiltrated pathogens

We consider EASI as the treatment outcome that will be compared directly to the data from clinical trials.

EASI score (ranging from 0 to 72), is calculated using the severity and the area scores of equally weighted four AD signs (erythema, induration, excoriations, and lichenification) on four body regions (head/neck, trunk, upper limbs, and lower limbs)³⁰. In our model, EASI score, $e(t)$, is described (FIGURE S4) by

$$e(t) = 72 \frac{2p(t)+2(1-s(t))}{4}, \quad (\text{S3})$$

where 72 is the maximal EASI score, $p(t)$ is the concentration of infiltrated pathogens with a

range from 0 (pathogen-free) to 1 (maximal infiltration) at t , and $s(t)$ is the level of skin barrier integrity with a range from 0 (complete destruction) to 1 (healthy state) at t . Extents of two AD signs (erythema and induration) and those of remaining two signs (excoriations and lichenification) were surrogated by $p(t)$ and $1 - s(t)$, respectively, as described below. We set $e(0) = 29.3$, the baseline EASI score of the participants in the dupilumab clinical trial, which was used as a reference value to normalize EASI scores in all clinical trials.

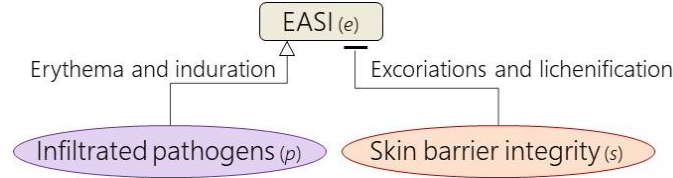


FIGURE S4 Relationship between EASI score and infiltrated pathogens and skin barrier integrity in our model.

We assumed erythema and induration correlate with the infiltrated pathogen load ($p(t)$) because these two signs can be induced by *Staphylococcus aureus*³¹, which is commonly colonized in AD skin lesion³². Erythema is caused by inflammatory vasodilation by histamines³³. Histamine is released mainly from mast cells that are activated by detecting infiltrated pathogens as antigens through antigen-specific IgE³⁴. Although both infiltrated pathogens and IgE play a role in this process, we associated the released histamine concentration with infiltrated pathogens load in this model because the amount of histamine release is more dependent on the amount of antigens than that of IgE³⁵. Low contribution of IgE on the AD pathogenesis is also suggested by a lack of clinical efficacy demonstrated for omalizumab (IgE neutralizing anti-IgE antibody). The other two signs, excoriations and lichenification are caused by scratching³⁶, which damages skin barrier integrity. The degree of damage of the skin barrier integrity is described by $1 - s(t)$.

The dynamics of $s(t)$ and $p(t)$ that determine $e(t)$ are described below.

(a) Skin barrier integrity

The dynamics of the skin barrier integrity, $s(t)$, is described (FIGURE S5) by

$$\frac{ds(t)}{dt} = \frac{(1-s(t))(k_1 + k_2 c_{22}(t) + k_3)}{(1+b_1 c_4(t))(1+b_2 c_{13}(t))(1+b_3 c_{17}(t))(1+b_4 c_{22}(t))(1+b_5 c_{31}(t))} - s(t)\{d_1(1 + d_3 p(t)) + d_2 c_{31}(t)\}, \quad (\text{S4})$$

where $c_4(t)$, $c_{13}(t)$, $c_{17}(t)$, $c_{22}(t)$, and $c_{31}(t)$ are the concentrations of IL-4, IL-13, IL-17A, IL-22, and IL-31, respectively, k_1 , k_2 , and k_3 are the recovery rates of skin barrier integrity via skin turnover, IL-22, and placebo effects, respectively, d_1 , d_2 , and d_3 are the degradation rates of skin barrier via skin turnover, IL-31, and infiltrated pathogens, respectively, and b_1 , b_2 , b_3 , b_4 , and b_5 correspond to the inhibitory strengths for recovery of skin barrier via IL-4, IL-13, IL-17A, IL-22, and IL-31, respectively. Levels of skin barrier integrity were defined between 0 (completely damaged) and 1 (healthy).

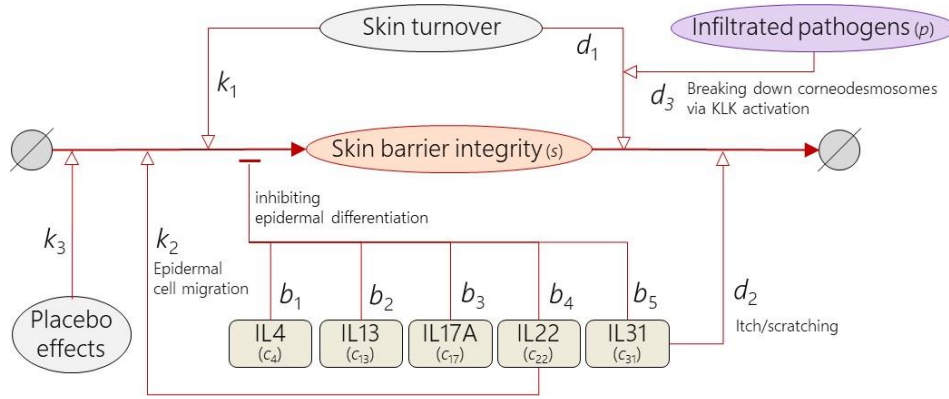


FIGURE S5 Regulation of skin barrier integrity level

Our model assumes that skin barrier integrity recovers by skin turnover (with the recovery rate, k_1), epidermal cell migration (k_2), and placebo effects (k_3). We assumed that skin turnover occurs independently from external perturbation and epidermal cell migration is promoted by IL-22³⁷. The placebo effect was applied to the models for both placebo- and drug-treated groups, as placebo-treated patients demonstrated improvement of the EASI score, presumably because of the controlled care for AD patients with concomitant drugs such as emollients in the clinical trials.

We modelled compromise the recovery of skin barrier integrity by IL-4³⁸ (with the strength b_1), IL-13³⁹ (b_2), IL-17A⁴⁰ (b_3), IL-22³⁷ (b_4), and IL-31⁴¹ (b_5), as they are shown to decrease filaggrin production and inhibit epidermal differentiation.

We also modelled degradation of the skin barrier by skin turnover (with the degradation rate d_1) and scratching through itch induced by IL-31 (d_2)⁴². Our model assumed that the impairment of skin barrier by skin turnover (d_1) is potentiated by infiltrated pathogens (d_3), such as *Staphylococcus aureus*, as *Staphylococcus aureus* stimulates TLR2⁴³ and thereby excessively activates KLR5⁴⁴ to increase desquamation in the skin turnover process⁴⁵.

(b) Infiltrated pathogens

The dynamics of the infiltrated pathogens, $p(t)$, is described (FIGURE S6) by

$$\frac{dp(t)}{dt} = \frac{k_4}{1+b_6s(t)} - p(t) \left\{ \frac{(1+d_4p(t))(1+d_5c_{17}(t))(1+d_6c_{22}(t))(1+d_7c_g(t))}{(1+b_7c_4(t))(1+b_8c_{13}(t))} + d_8 \right\}, \quad (S5)$$

where k_4 is the rate of pathogen infiltration, d_4 , d_5 , d_6 , d_7 , and d_8 are the elimination rates of infiltrated pathogens via infiltrated pathogens themselves, IL-17A, IL-22, IFN γ (these factors increase release of AMPs as described below), and skin turnover, respectively, b_6 corresponds to the inhibitory strength for pathogens infiltration via skin barrier, b_7 and b_8 correspond to the inhibitory strengths for elimination of infiltrated pathogens via IL-4 and IL-13, respectively, and $c_g(t)$ is the concentration of IFN γ . Levels of the infiltrated pathogens were defined between 0 (pathogen-free) and 1 (maximal infiltration).

We assumed that the steady-state infiltrated pathogen level is 1 (the maximal level of infiltrated pathogens when $\frac{dp(t)}{dt} = 0$) if skin barrier integrity is destructed completely ($s(t) = 0$) and the effects of AMP to decrease infiltrated pathogens is zero ($\frac{(1+d_4p(t))(1+d_5c_{17}(t))(1+d_6c_{22}(t))(1+d_7c_g(t))}{(1+b_7c_4(t))(1+b_8c_{13}(t))} \cong 0$) at the steady-state. This condition leads to $k_4 = d_8$.

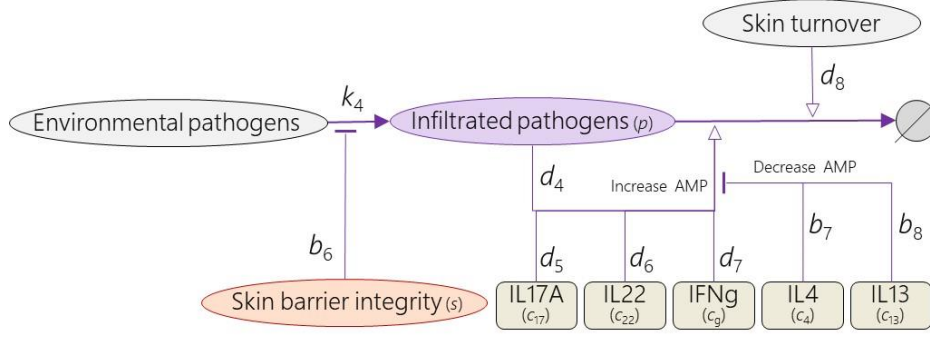


FIGURE S6 Regulation of infiltrated pathogen level

The infiltrated pathogens increase by penetration of environmental pathogens through the skin barrier (with the rate k_4), whose integrity determines how easily pathogens can infiltrate (with strength b_6). Microbial pathogens are killed by AMP directly⁴⁶. IL-17A⁴⁷, IL-22⁴⁸, and IFNg⁴⁹ increase AMP release from keratinocytes (with the strengths, d_5 , d_6 and d_7 , respectively), whereas the infiltrated pathogens, such as *Staphylococcus aureus*, also increase AMP release from keratinocytes via other pathways independent to these cytokines⁵⁰ (d_4). IL-4 and IL-13 inhibit the AMP release⁴⁹ (with the strengths b_7 and b_8). The infiltrated pathogens decrease due to the skin turnover (d_8).

3.2. Cytokines

The dynamics of the cytokines and OX40L, $c_4(t)$, $c_{13}(t)$, $c_{17}(t)$, $c_{22}(t)$, $c_{31}(t)$, $c_g(t)$, $c_{TS}(t)$, and $c_{OX}(t)$ are described (FIGURE S7) by

$$\frac{dc_4(t)}{dt} = k_{11}c_{t2}(t) + k_{12} - d_{10}c_4(t), \quad (S6)$$

$$\frac{dc_{13}(t)}{dt} = k_{13}c_{t2}(t) + k_{14} - d_{11}c_{13}(t), \quad (S7)$$

$$\frac{dc_{17}(t)}{dt} = k_{15}c_{t17}(t) + k_{16} - d_{12}c_{17}(t), \quad (S8)$$

$$\frac{dc_{22}(t)}{dt} = k_{17}c_{t22}(t) + k_{18} - d_{13}c_{22}(t), \quad (S9)$$

$$\frac{dc_{31}(t)}{dt} = k_{19}c_{t2}(t) + k_{20} - d_{14}c_{31}(t), \quad (S10)$$

$$\frac{dc_g(t)}{dt} = k_{21}c_{t1}(t) + k_{22} - d_{15}c_g(t), \quad (S11)$$

$$\frac{dc_{TS}(t)}{dt} = k_{23}p(t) + k_{24} - d_{16}c_{TS}(t), \quad (S12)$$

$$\frac{dc_{OX}(t)}{dt} = k_{25}c_{TS}(t) + k_{26} - d_{17}c_{OX}(t), \quad (S13)$$

where $c_{TS}(t)$ is the concentrations of TSLP and $c_{OX}(t)$ is the level of OX40L, k_{11} is the IL-4 secretion rate via Th2, k_{13} is the IL-13 secretion rate via Th2, k_{15} is the IL-17A secretion rate via Th17, k_{17} is the IL-22 secretion rate via Th22, k_{19} is the IL-31 secretion rate via Th2, k_{21} is the IFNg secretion rate via Th1, k_{23} is the TSLP secretion rate via infiltrated pathogens, k_{25} is the OX40L expression rate via TSLP, d_{10} , d_{11} , d_{12} , d_{13} , d_{14} , d_{15} , d_{16} , and d_{17} are the elimination rates for IL-4, IL-13, IL-17A, IL-22, IL-31, IFNg, TSLP, and OX40L, respectively, and k_{12} , k_{14} , k_{16} , k_{18} , k_{20} , k_{22} , k_{24} , and k_{26} are the secretion or expression rates of IL-4, IL-13, IL-17A, IL-22, IL-31, IFNg, TSLP, and OX40L via other pathways that were not explicitly considered in the model.

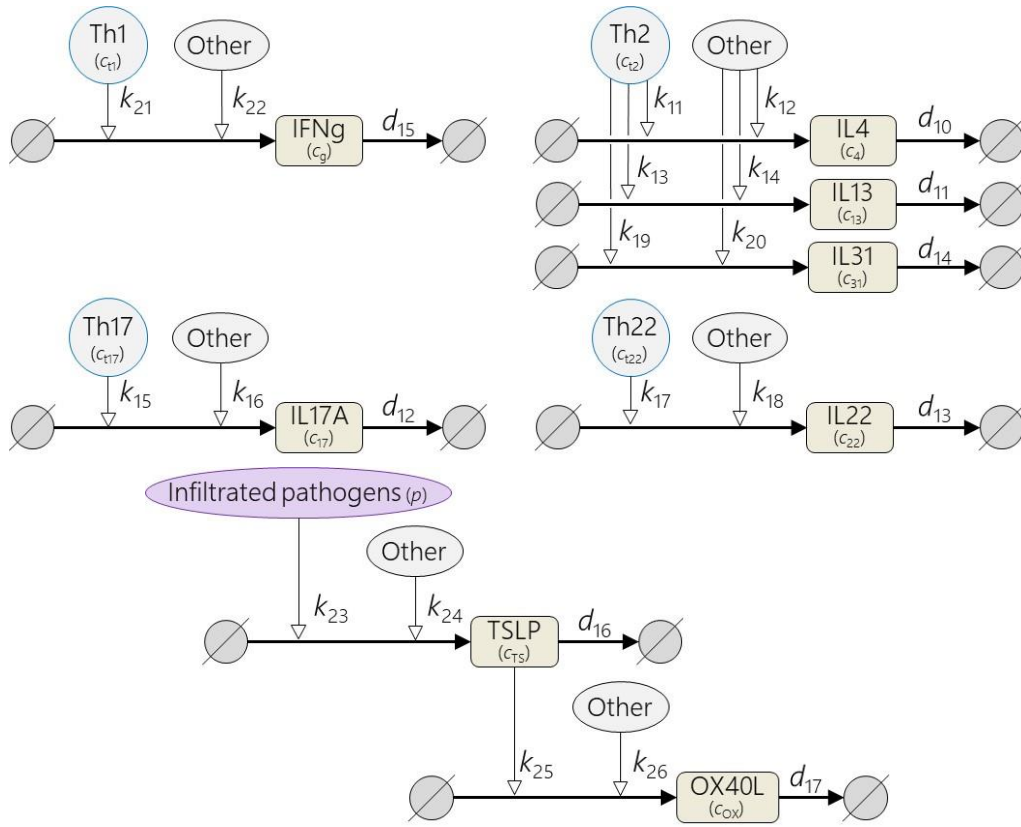


FIGURE S7 Modelling of regulation of cytokine concentrations

Th1 secretes IFNg⁵¹ (with the rate k_{21}), while Th2 secretes IL-4⁵², IL-13⁵¹, and IL31⁵³ (with the rates k_{11} , k_{13} , and k_{19}). Th17 and Th22 produce IL17A⁵² and IL-22⁵⁴ (with the rates k_{15} and k_{17}). Infiltrated pathogens induce TSLP in keratinocytes through TLR2 pathway⁵⁵ (with the rate k_{23}), and TSLP induces DCs to express OX40L⁵⁶ (with the rate k_{26}). There are other pathways releasing cytokines, which were implicitly described as “other” effects (with the rates k_{12} , k_{14} , k_{16} , k_{18} , k_{20} , k_{22} , k_{24} , k_{26}).

3.3. T cells

The dynamics of the concentrations of Th1, Th2, Th17, and Th22 cells, $c_{t1}(t)$, $c_{t2}(t)$, $c_{t17}(t)$, and $c_{t22}(t)$, are described (FIGURE S8) by

$$\frac{dc_{t1}(t)}{dt} = k_5 p(t) \left(\frac{1+k_9 c_g(t)}{4+k_9 c_g(t)+k_{10} c_4(t)} \right) - \frac{d_9 c_{t1}(t)}{1+b_9 c_{OX}(t)}, \quad (S14)$$

$$\frac{dc_{t2}(t)}{dt} = k_6 p(t) \left(\frac{1+k_{10} c_4(t)}{4+k_9 c_g(t)+k_{10} c_4(t)} \right) - \frac{d_9 c_{t2}(t)}{1+b_9 c_{OX}(t)}, \quad (S15)$$

$$\frac{dc_{t17}(t)}{dt} = k_7 p(t) \left(\frac{1}{4+k_9 c_g(t)+k_{10} c_4(t)} \right) - \frac{d_9 c_{t17}(t)}{1+b_9 c_{OX}(t)}, \quad (S16)$$

$$\frac{dc_{t22}(t)}{dt} = k_8 p(t) \left(\frac{1}{4+k_9 c_g(t)+k_{10} c_4(t)} \right) - \frac{d_9 c_{t22}(t)}{1+b_9 c_{OX}(t)}, \quad (S17)$$

where k_5 , k_6 , k_7 , and k_8 are the rates of differentiation of naïve T cells to Th1, Th2, Th17, and Th22, respectively, k_9 and k_{10} are the strengths of polarization for Th1 and Th2 differentiation, respectively, d_9 is the T cell elimination rate, b_9 is the inhibitory strength for T cells elimination by OX40L.

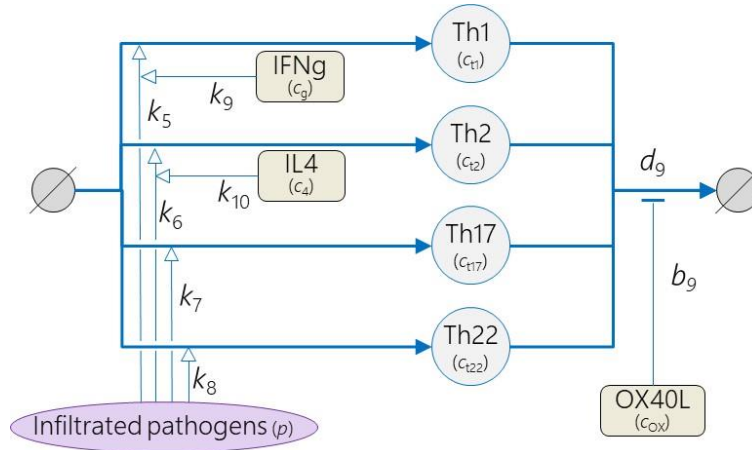


FIGURE S8 Regulation of T-cell concentrations

Concentration of Th1, Th2, Th17, and Th22 cells increases via differentiation of naïve T cells⁵⁷ that are primed by dendritic cells (DCs) activated by the infiltrated pathogen⁵⁸ (with the rate k_5 , k_6 , k_7 and k_8 , respectively). The balance of the differentiation into each T cell subset depends on the cytokine environment⁵⁹; IFNg drives Th1 polarization⁶⁰ (with the strength k_9) while IL-4 promotes differentiation toward Th2⁶¹ (k_{10}). Preferential polarization of certain helper-T cell subset reduces room for other subsets to be differentiated (Th1 : Th2 : Th17 : Th22 = $(1 + k_9 c_g(t)) : (1 + k_{10} c_4(t)) : 1 : 1$ with ratio to the sum of all the subtypes: $1 + k_9 c_g(t) + 1 + k_{10} c_4(t) + 1 + 1 = 4 + k_9 c_g(t) + k_{10} c_4(t)$). The T cells decrease according to their turnover (with the rate d_9). OX40L promotes prolongation of T cell activation and survival (with the strength b_9) as it activates the tumor necrosis factor receptor OX40, and functions as a T-cell costimulatory factor⁶².

3.4. Drug effects

We described the effects of the antibodies that inhibit the target signaling by scaling the actual concentrations of the target cytokines or OX40L by an inhibitory rate, r_{inhibit} , for each drug (Eq. 2 and TABLE S3).

r_{inhibit} of each drug was defined using the half maximal inhibitory concentration (IC_{50}) of the drug against the target biological factor and the mean concentration of drugs in the skin⁶³ (d_{skin}) by

$$r_{\text{inhibit}} = \begin{cases} \frac{d_{\text{skin}}}{IC_{50} + d_{\text{skin}}} e_{a2}, & \text{if drug is tralokinumab,} \\ \frac{d_{\text{skin}}}{IC_{50} + d_{\text{skin}}}, & \text{otherwise,} \end{cases} \quad (\text{S18})$$

where e_{a2} represents the inhibitory effects of IL-13 binding to IL-13R α 2 in tralokinumab. d_{skin} is defined by $r_{\text{skin/serum}} d_{\text{serum}}$, where $r_{\text{skin/serum}}$ is a ratio of drug concentration in the skin to that in serum and d_{serum} is the mean concentration of the drug in serum. We adopted $r_{\text{skin/serum}} = 0.157$ for all the antibodies based on the estimated ratio of antibody concentration in the skin to that in the plasma⁶⁴. Values of IC_{50} and d_{serum} (TABLE S3) were obtained from reported results of in vitro assay and the reported pharmacokinetics data of the adopted dose regimen (TABLE 1) in clinical trials.

We introduced e_{a2} for tralokinumab because tralokinumab not only inhibits IL-13 signaling via IL-13R α 1 but also enhances IL-13 signaling via inhibition of IL-13 binding to IL-13R α 2. IL-13R α 1 forms a heterodimeric receptor with IL-4R α and is related to the effects of IL-13

signaling in AD pathogenesis. IL-13R α 2 is a decoy receptor to decrease IL-13 signaling via IL-13R α 1. Hence, the influence of the inhibition of IL-13R α 2 in tralokinumab was described by e_{a2} to scale down the r_{inhibit} based on the IC₅₀ against IL-13R α 1. On the other hand, lebrikizumab prevents IL-13 from binding to IL-13R α 1 only⁶⁵. We adopted $e_{a2} = 0.44$ so that it reproduces the differences of %improved EASI and EASI-75 between tralokinumab and lebrikizumab (FIGURE 3).

We also described the effects of rIFNg that replaces the target cytokine (IFNg) by estimating the mean concentration, c_{rIFNg} , of rIFNg in the skin (TABLE S3). c_{rIFNg} was estimated using the reported mean concentration of IFNg in the serum after rIFNg administration and the estimated ratio of rIFNg concentration in the skin to that in the plasma⁶⁶ by

$$c_{\text{rIFNg}} = \frac{r_{\text{IFNg_skin/serum}} d_{\text{rIFNg_serum}}}{d_{\text{IFNg_skin}}}, \quad (\text{S19})$$

where $d_{\text{rIFNg_serum}}$ is the mean concentration of rIFNg in serum after the rIFNg administration (i.e., the increased concentration of IFNg), $r_{\text{IFNg_skin/serum}}$ and $d_{\text{IFNg_skin}}$ are a ratio of rIFNg concentration in the skin to that in serum and mean concentration of IFNg in the skin in the observational study, respectively. $d_{\text{rIFNg_serum}}$ and $d_{\text{IFNg_skin}}$ were obtained from the pharmacokinetics data of rIFNg⁶⁷ and the IFNg concentration in the healthy skin in the observational study⁶⁸, respectively. We adopted $r_{\text{IFNg_skin/serum}} = 1.60$ based on the estimated ratio of macromolecule concentration in the skin to that in the plasma⁶⁶.

TABLE S3 Parameter values for effects of drugs used in this study

Drugs	IC ₅₀ (mcg/mL)	$d_{\text{skin}}/d_{\text{serum}}$ or $d_{\text{rIFNg_skin}}/d_{\text{rIFNg_serum}}$ (mcg/mL)	r_{inhibit}								c_{rIFNg} (fold change against healthy skin)
			IL-4	IL-13	IL-17A	IL-22	IL-31	TSLP	OX40L	IFNg	
Dupilumab ^{69, 70}	IL-4: <0.01 IL-13: 0.01	183/29	0.99	0.99	-	-	-	-	-	-	-
Nemolizumab ^{71,72}	0.01	6/1	-	-	-	-	0.99	-	-	-	-
Tezepelumab ^{73, 74}	0.21	109/17	-	-	-	-	-	0.99	-	-	-
GBR 830 ^{75, 76}	0.13	90/14	-	-	-	-	-	-	0.99	-	-
Fezakinumab ^a	-	-	-	-	-	0.99	-	-	-	-	-
Secukinumab ^{77,78}	0.08	45/7	-	-	0.99	-	-	-	-	-	-
Tralokinumab ^{65, 79}	0.10	70/11	-	0.99 e_{a2}	-	-	-	-	-	-	-
Lebrikizumab ^{80 b}	0.10	91/14	-	0.99	-	-	-	-	-	-	-
rIFNg ⁶⁷	-	4.0E-6 /5.3E-4	-	-	-	-	-	-	-	2.1E2	-

a: IC₅₀ and mean concentration were not found in published literature. We assumed an almost complete inhibition (the 99% inhibition as the same as other antibodies) for fezakinumab. b: IC₅₀ and mean concentration were not found in the publication. We assumed that tralokinumab and lebrikizumab have the equivalent IC₅₀ because their mechanisms of binding are similar⁶⁵ and that the mean drug concentration of 250 mg q2w is four times larger than that of 125 mg q4w (reported mean drug concentration is 22.8 mcg/mL).

4. Model parameters

We selected 102 parameters of the distributions (μ_n and σ_n that define the distributions of the 51 parameters, TABLE S4) by

- 1) calculating μ_n of elimination rates for 11 biological factors based on available data and assumptions, and
- 2) tuning the remaining 91 parameter values so that the model reproduces clinical data.

TABLE S4 Optimal parameter values obtained by parameter tuning

Parameters	μ_n	σ_n	Comments
k_1 Recovery rate of skin barrier integrity via skin turnover	0.54	0.79	-
k_2 Recovery rate of skin barrier integrity via IL-22	-1.50	0.39	-
k_3 Recovery rate of skin barrier integrity via placebo effects	2.95	1.42	-
k_4 Rate of pathogen infiltration	-	-	$k_4 = d_8$ (Section S3.1 (b))
k_5 Rate of differentiation of naïve T cells to Th1	2.95	0.04	-
k_6 Rate of differentiation of naïve T cells to Th2	3.89	0.00	-
k_7 Rate of differentiation of naïve T cells to Th17	2.60	0.07	-
k_8 Rate of differentiation of naïve T cells to Th22	4.83	0.48	-
k_9 Strength of polarization for Th1 differentiation	-3.32	0.99	-
k_{10} Strength of polarization for Th2 differentiation	-5.82	0.07	-
k_{11} IL-4 secretion rate via Th2	5.50	0.16	-
k_{12} IL-4 secretion rate via other pathways	9.25	0.51	-
k_{13} IL-13 secretion rate via Th2	6.65	0.37	-
k_{14} IL-13 secretion rate via other pathways	8.84	0.45	-
k_{15} IL-17A secretion rate via Th17	4.01	0.27	-
k_{16} IL-17A secretion rate via other factors	2.64	0.85	-
k_{17} IL-22 secretion rate via Th22	1.19	0.21	-
k_{18} IL-22 secretion rate via other factors	1.46	0.03	-
k_{19} IL-31 secretion rate via Th2	1.54	0.19	-
k_{20} IL-31 secretion rate via other factors	1.99	0.58	-
k_{21} IFN γ secretion rate via Th1	0.46	1.00	-
k_{22} IFN γ secretion rate via other factors	2.62	0.35	-
k_{23} TSLP secretion rate via infiltrated pathogens	4.00	0.52	-
k_{24} TSLP secretion rate via other factors	4.43	0.65	-
k_{25} OX40L expression rates via TSLP	0.42	0.48	-
k_{26} OX40L expression rates via other factors	1.68	0.78	-
b_1 Inhibitory strength for recovery of skin barrier via IL-4	-8.69	0.57	-
b_2 Inhibitory strength for recovery of skin barrier via IL-13	-3.54	1.58	-
b_3 Inhibitory strength for recovery of skin barrier via IL-17	-3.92	0.35	-
b_4 Inhibitory strength for recovery of skin barrier via IL-22	-0.59	0.80	-
b_5 Inhibitory strength for recovery of skin barrier via IL-31	-2.09	0.90	-
b_6 inhibitory strength for pathogens infiltration via skin barrier	0.39	0.44	-
b_7 Inhibitory strength for elimination of infiltrated pathogens via IL-4	-7.99	0.09	-
b_8 Inhibitory strength for elimination of infiltrated pathogens via IL-13	-3.50	0.05	-
b_9 Inhibitory strength for T cells elimination by OX40L	-2.66	0.30	-
d_1 Degradation rate of skin barrier via skin turnover	-1.60	1.53	μ_n based on half-live (TABLE S5)
d_2 Degradation rate of skin barrier via IL-31	-2.64	0.57	-
d_3 Degradation rate of skin barrier via infiltrated pathogens	1.25	2.28	-
d_4 Elimination rate of infiltrated pathogens via infiltrated pathogens themselves	-1.00	0.47	-
d_5 Elimination rate of infiltrated pathogens via IL-17A	-5.10	0.45	-
d_6 Elimination rate of infiltrated pathogens via IL-22	-5.01	0.39	-
d_7 Elimination rate of infiltrated pathogens via IFN γ	-8.70	0.62	-
d_8 Elimination rate of infiltrated pathogens via skin turnover	-1.60	0.04	μ_n based on half-live (TABLE S5)
d_9 T cell elimination rate	-0.55	0.09	μ_n based on half-live (TABLE S5)
d_{10} Elimination rates for IL-4	5.91	0.22	μ_n based on half-live (TABLE S5)
d_{11} Elimination rates for IL-13	5.91	0.11	μ_n based on half-live (TABLE S5)
d_{12} Elimination rates for IL-17A	3.33	0.57	μ_n based on half-live (TABLE S5)
d_{13} Elimination rates for IL-22	3.33	0.56	μ_n based on half-live (TABLE S5)
d_{14} Elimination rates for IL-31	3.33	0.10	μ_n based on half-live (TABLE S5)
d_{15} Elimination rates for IFN γ	2.68	0.15	μ_n based on half-live (TABLE S5)
d_{16} Elimination rates for TSLP	3.33	0.20	μ_n based on half-live (TABLE S5)
d_{17} Elimination rates for OX40L	0.48	0.24	μ_n based on half-live (TABLE S5)

4.1. μ_n of elimination rates calculated with published data and assumptions

The elimination rates of the 11 biological factors were determined using the half-lives measured in vivo (serum) in humans (TABLE S5). The calculated values were set as the μ_n ,

the mean value for each distribution.

TABLE S5 Elimination rates of biological factors used in this study

Parameters	Biological factors	Elimination rate (/week)	Half-life (week)	Comments on half-lives
d_1	Skin barrier integrity	0.202	3.4^{81}	Based on the half-life of the epidermis
d_8	Infiltrated pathogens	0.202	3.4^{81}	Based on the half-life of the epidermis
d_9	Th1	0.578	1.2^{82}	-
	Th2			
	Th17			
	Th22			
d_{10}	IL-4	368	$1.9\text{E-}03^{83}$	-
d_{11}	IL-13	368	$1.9\text{E-}03$	Assumed same as IL-4 because IL-4 and IL-13 are the same IL-2 sub-family
d_{12}	IL-17A	28.0	$2.5\text{E-}02$	Assumed mean value of IL-4 and IFNg as average cytokine
d_{13}	IL-22	28.0	$2.5\text{E-}02$	Assumed mean value of IL-4 and IFNg as average cytokine
d_{14}	IL-31	28.0	$2.5\text{E-}02$	Assumed mean value of IL-4 and IFNg as average cytokine
d_{15}	IFNg	14.6	$4.8\text{E-}02^{84}$	-
d_{16}	TSLP	28.0	$2.5\text{E-}02$	Assumed mean value of IL-4 and IFNg as average cytokine
d_{17}	OX40L	1.62	0.4^{85}	Based on dendritic cells of mouse data. OX40L are expressed on dendritic cells.

4.2. Parameters tuned to reproduce clinical data

The remaining 91 parameters were tuned so that the model reproduces the following clinical data consisting of 136 reference values;

- mean values and coefficient of variation (%CV) of 12 biological factors (IL-4, IL-13, IL-17A, IL-22, IL-31, IFNg, TSLP, OX40L, Th1, Th2, Th17, and Th22) in observational studies and baseline EASI score in clinical trial of dupilumab (TABLE S2. 2 indices x 13 factors = 26 reference values) and
- mean EASI score and EASI-75 when 9 drugs and placebo were applied in clinical trials (FIGURE 1. 2 indices x 10 interventions x 1-10 time points/intervention = 110 reference values).

We searched the parameters that minimizes the cost function, J , defined by

$$J = w_1 J_1 + w_2 J_2 + w_3 J_3 + w_4 J_4, \quad (\text{S18})$$

where

$$J_1 = \sqrt{\frac{1}{l} \sum_{h=1}^l (u_h - \hat{u}_h)^2}, \quad (\text{S19})$$

$$J_2 = \sqrt{\frac{1}{l} \sum_{h=1}^l (v_h - \hat{v}_h)^2}, \quad (\text{S20})$$

$$J_3 = \sqrt{\frac{1}{n} \sum_{i=1}^n \left\{ \frac{1}{m} \sum_{j=1}^m w_T \left(a_i(t_j) - \hat{a}_i(t_j) \right) \right\}^2}, \quad (\text{S21})$$

$$J_4 = \sqrt{\frac{1}{n} \sum_{i=1}^n \left\{ \frac{1}{m} \sum_{j=1}^m w_T \left(b_i(t_j) - \hat{b}_i(t_j) \right) \right\}^2}. \quad (\text{S22})$$

The terms, J_1 and J_2 are root mean squared errors of mean values and %CV of biological factors, respectively. J_3 and J_4 are weighted root mean squared errors of mean EASI score

and EASI-75, respectively. w_1 to w_4 are the weighting coefficients. u_h and v_h are the mean value and the %CV of the h -th biological factor ($h=1, \dots, l$) in the observational studies. $\hat{u}_h$ and $\hat{v}_h$ are the corresponding values among 1000 virtual patients in the simulation at the steady-state (after 1000 weeks). $a_i(t_j)$ and $b_i(t_j)$ are the reference value of the mean EASI score and of EASI-75 in the study using the i -th drug ($i=1, \dots, n$) at time t_j ($j=1, \dots, m$) with the weighting for time points, w_T . $\hat{a}_i(t_j)$ and $\hat{b}_i(t_j)$ are the corresponding simulated values.

We used $(w_1, w_2, w_3, w_4) = (10, 1, 1, 1)$ and $w_T = \begin{cases} 1 & (t_j < 8) \\ 10 & (t_j \geq 8) \end{cases}$. We set a higher weight on the mean values of the biological factors, w_1 , because its fitting error tends to be smaller than other items (ie, %CV of the biological factors, the mean EASI score, and EASI-75). We also set a higher weight on the time points of 8 weeks or later, w_T , because the efficacies are evaluated at least after 8 weeks as primary endpoints in the clinical trials⁸⁶.

Parameter tuning was based on differential evolution⁸⁷, which is known to be an effective method for global optimization of a large number of parameters. The conditions for differential evolution were set as follows based on manual trial-and-error.

Mutation constant (F)	: 0.5
Crossover constant (CR)	: 0.7
Strategy	: DE/best/1/bin
Number of population vectors (NP)	: 92
Number of function evaluations (nfe)	: 46092
Ranges of parameters searched	: TABLE S6

We tuned both the 91 parameters of the distributions and e_{a2} (92 parameters in total) at once. J was minimized to 27.1, where the model fitness was confirmed visually (FIGURE 3).

As reference information, we also calculated (not-weighted) root mean squared errors of mean EASI score and EASI-75 by

$$J_5 = \sqrt{\frac{1}{n} \sum_{i=1}^n \left\{ \frac{1}{m} \sum_{j=1}^m (a_i(t_j) - \hat{a}_i(t_j)) \right\}^2}, \quad (\text{S23})$$

$$J_6 = \sqrt{\frac{1}{n} \sum_{i=1}^n \left\{ \frac{1}{m} \sum_{j=1}^m (b_i(t_j) - \hat{b}_i(t_j)) \right\}^2}. \quad (\text{S24})$$

TABLE S6 Ranges of parameters searched in parameter tuning

Parameters	μ_n	σ_n	Comments
k_1 Recovery rate of skin barrier integrity via skin turnover	[0, 1]	[0, 1]	-
k_2 Recovery rate of skin barrier integrity via IL-22	[-2, -1]	[0, 1]	-
k_3 Recovery rate of skin barrier integrity via placebo effects	[2, 3]	[1, 2]	-
k_4 Rate of pathogen infiltration	-	-	$k_4 = d_8$ (Section S3.1 (b))
k_5 Rate of differentiation of naïve T cells to Th1	[2, 3]	[0, 1]	-
k_6 Rate of differentiation of naïve T cells to Th2	[3, 4]	[0, 1]	-
k_7 Rate of differentiation of naïve T cells to Th17	[2, 3]	[0, 1]	-
k_8 Rate of differentiation of naïve T cells to Th22	[4, 5]	[0, 1]	-
k_9 Strength of polarization for Th1 differentiation	[-4, -3]	[0, 1]	-
k_{10} Strength of polarization for Th2 differentiation	[-6, -5]	[0, 1]	-
k_{11} IL-4 secretion rate via Th2	[5, 6]	[0, 1]	-
k_{12} IL-4 secretion rate via other pathways	[9, 10]	[0, 1]	-
k_{13} IL-13 secretion rate via Th2	[6, 7]	[0, 1]	-
k_{14} IL-13 secretion rate via other pathways	[8, 9]	[0, 1]	-
k_{15} IL-17A secretion rate via Th17	[4, 5]	[0, 1]	-
k_{16} IL-17A secretion rate via other factors	[2, 3]	[0, 1]	-
k_{17} IL-22 secretion rate via Th22	[1, 2]	[0, 1]	-
k_{18} IL-22 secretion rate via other factors	[1, 2]	[0, 1]	-
k_{19} IL-31 secretion rate via Th2	[1, 2]	[0, 1]	-
k_{20} IL-31 secretion rate via other factors	[1, 2]	[0, 1]	-
k_{21} IFN γ secretion rate via Th1	[0, 1]	[1, 2]	-
k_{22} IFN γ secretion rate via other factors	[2, 3]	[0, 1]	-
k_{23} TSLP secretion rate via infiltrated pathogens	[4, 5]	[0, 1]	-
k_{24} TSLP secretion rate via other factors	[4, 5]	[0, 1]	-
k_{25} OX40L expression rates via TSLP	[0, 1]	[0, 1]	-
k_{26} OX40L expression rates via other factors	[1, 2]	[0, 1]	-
b_1 Inhibitory strength for recovery of skin barrier via IL-4	[-9, -8]	[0, 1]	-
b_2 Inhibitory strength for recovery of skin barrier via IL-13	[-4, -3]	[1, 2]	-
b_3 Inhibitory strength for recovery of skin barrier via IL-17	[-4, -3]	[0, 1]	-
b_4 Inhibitory strength for recovery of skin barrier via IL-22	[-1, 0]	[0, 1]	-
b_5 Inhibitory strength for recovery of skin barrier via IL-31	[-3, -2]	[0, 1]	-
b_6 inhibitory strength for pathogens infiltration via skin barrier	[0, 1]	[0, 1]	-
b_7 Inhibitory strength for elimination of infiltrated pathogens via IL-4	[-8, -7]	[0, 1]	-
b_8 Inhibitory strength for elimination of infiltrated pathogens via IL-13	[-4, -3]	[0, 1]	-
b_9 Inhibitory strength for T cells elimination by OX40L	[-3, -2]	[0, 1]	-
d_1 Degradation rate of skin barrier via skin turnover	-	[1, 2]	μ_n based on half-live (TABLE S5)
d_2 Degradation rate of skin barrier via IL-31	[-3, -2]	[0, 1]	
d_3 Degradation rate of skin barrier via infiltrated pathogens	[1, 2]	[2, 3]	-
d_4 Elimination rate of infiltrated pathogens via infiltrated pathogens themselves	[-2, -1]	[0, 1]	-
d_5 Elimination rate of infiltrated pathogens via IL-17A	[-6, -5]	[0, 1]	-
d_6 Elimination rate of infiltrated pathogens via IL-22	[-6, -5]	[0, 1]	-
d_7 Elimination rate of infiltrated pathogens via IFN γ	[-9, -8]	[0, 1]	-
d_8 Elimination rate of infiltrated pathogens via skin turnover	-	[0, 1]	μ_n based on half-live (TABLE S5)
d_9 T cell elimination rate	-	[0, 1]	μ_n based on half-live (TABLE S5)
d_{10} Elimination rates for IL-4	-	[0, 1]	μ_n based on half-live (TABLE S5)
d_{11} Elimination rates for IL-13	-	[0, 1]	μ_n based on half-live (TABLE S5)
d_{12} Elimination rates for IL-17A	-	[0, 1]	μ_n based on half-live (TABLE S5)
d_{13} Elimination rates for IL-22	-	[0, 1]	μ_n based on half-live (TABLE S5)
d_{14} Elimination rates for IL-31	-	[0, 1]	μ_n based on half-live (TABLE S5)
d_{15} Elimination rates for IFN γ	-	[0, 1]	μ_n based on half-live (TABLE S5)
d_{16} Elimination rates for TSLP	-	[0, 1]	μ_n based on half-live (TABLE S5)
d_{17} Elimination rates for OX40L	-	[0, 1]	μ_n based on half-live (TABLE S5)

5. Influences of pathophysiological backgrounds of virtual patients on clinical efficacy

We investigated the influence of the 51 model parameters on %improve EASI of each drug using the LHS-PRCC (FIGURE 4), and simulated the %improve EASI at week 24 after patient stratification based on the baseline levels of cytokines in the skin (FIGURE S9) with regards to drugs other than dupilumab as well.

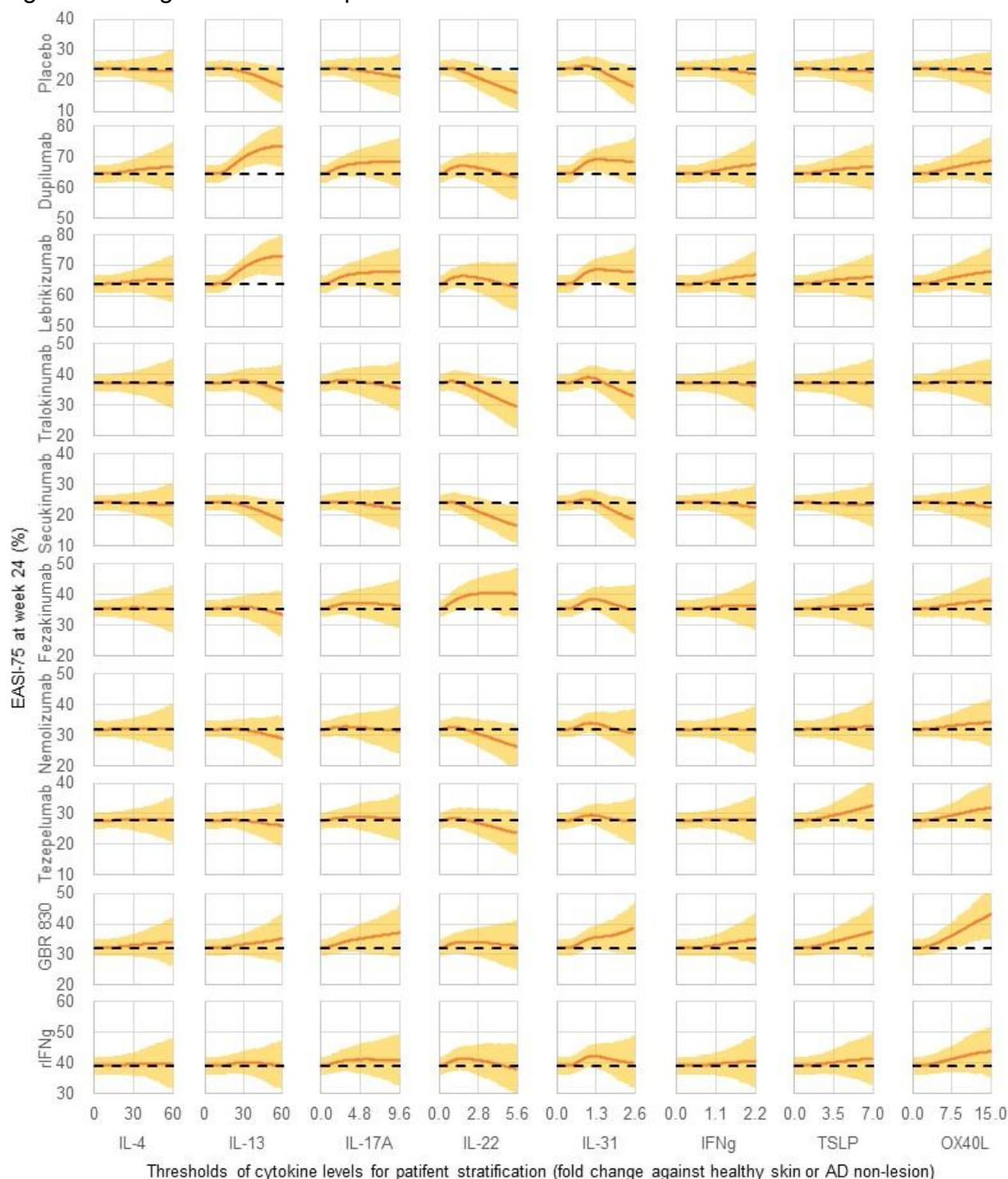


FIGURE S9 Simulated EASI-75 at 24 weeks after drug treatment (y-axis) for stratified patients with their cytokine baseline levels larger than the threshold values (x-axis)

The number of stratified virtual patients decreases for a larger threshold value. The threshold of zero includes all the virtual patients and the maximum threshold value corresponds to inclusion of at least 10% of 1000 virtual patients, who were generated according to the tuned distributions of the parameters (TABLE S4). Simulation was iterated 1000 times where a cohort of 1000 virtual patients were created at each iteration. Lines and

shaded areas are the mean value and 95% CI of 1000 simulations, respectively. The higher EASI-75 compared with that without patient stratification (with the threshold value of zero: dashed line) suggests a success in stratifying good responders.

5.1. Influence of skin barrier on placebo effects

Three skin barrier-related parameters (k_1 , k_3 , and b_6) had a significant PRCC with the efficacy in placebo group (FIGURE 4); these influences were also observed in all the drugs as the placebo effects were considered in both placebo- and drug-treated groups in the simulation.

The virtual patients with a lower k_1 and a higher k_3 benefited more from recovery of skin barrier via placebo effects, and thereby achieved a higher %improve EASI. The virtual patients with a higher b_6 inhibit pathogen infiltration more strongly through the recovery of skin barrier by placebo effects, and thereby achieved higher %improve EASI. These results may suggest that older patients whose skin has a slow baseline turnover (a lower k_1) but can inhibit pathogen infiltration (a higher b_6 , e.g., sufficient filaggrin functions to form skin barrier) are more responsive to placebo effects.

5.2. Influence of skin barrier on efficacy in multiple drugs in common

Four skin barrier-related parameters (b_2 , b_4 , d_1 , and d_3) had a significant PRCC with the %improved EASI by several drugs (FIGURE 4). These influences correspond to baseline severity of skin barrier defects rather than MoA of each drug.

Virtual patients with higher b_2 , b_4 , d_1 , and d_3 were more responsive to treatment by several drugs (i.e., dupilumab, lebrikizumab, fezakinumab, and rIFN γ) because they benefit from recovery of skin barrier via each drug MoA, achieving a higher %improve EASI. These results suggest that patients with a higher degradation rate of skin barrier via skin turnover (d_1 , e.g., activity of kallikreins to degrade skin barrier) and via infiltrated pathogens (d_3 , e.g., amounts of extracellular protease from *S. aureus* to degrade skin barrier), as well as a larger influence of cytokines on skin barrier damage (b_2 and b_4 correspond to IL-13 and IL-22), are more responsive to several drugs.

5.3. Influence of IL-13 level on efficacy in lebrikizumab and tralokinumab

The results for lebrikizumab and tralokinumab were similar to those about dupilumab as both drugs have the drug target IL-13 in common, although tralokinumab was less influenced by the IL-13-related parameters due to the lower inhibition rate of IL-13 than lebrikizumab (estimated 44% of lebrikizumab: $e_{a2} = 0.44$).

Ten model parameters had a significant PRCC with the %improved EASI by lebrikizumab (FIGURE 4). Four out of the ten parameters are IL-13-related (k_{13} , k_{14} , b_2 , and d_{11}), and the remaining six parameters are skin barrier-related parameters (k_1 , k_3 , b_4 , b_6 , d_1 , and d_3) that correspond to placebo effects and baseline severity of skin barrier defects rather than MoA of lebrikizumab.

The four IL-13 related parameters (k_{13} , k_{14} , b_2 , and d_{11}) characterize responders for lebrikizumab. Virtual patients with higher k_{13} , k_{14} , and b_2 and a lower d_{11} were more responsive to treatment by lebrikizumab. The parameters, k_{13} , k_{14} , and d_{11} , affect the IL-13 baseline level, and EASI-75 was improved by stratifying virtual patients with a higher IL-13 baseline level (FIGURE S9). The parameter, b_2 , describes the influence of IL-13 on skin barrier damage.

Four model parameters had a significant PRCC with the %improved EASI by tralokinumab (FIGURE 4). One out of the six parameters are IL-13-related (b_2), and the remaining five parameters are skin barrier-related parameters (k_1 , k_3 , and b_6) that correspond to placebo effects rather than MoA of tralokinumab.

Virtual patients with higher b_2 were more responsive to treatment by tralokinumab, although the extent was smaller than the case of lebrikizumab. As opposed to lebrikizumab, EASI-75 was not improved by stratifying virtual patients with a higher IL-13 baseline level (FIGURE S8).

5.4. Influence of IL-22 level on efficacy in fezakinumab

Eight model parameters had a significant PRCC with the %improved EASI by fezakinumab (FIGURE 4). Two out of the eight parameters are IL-22-related (b_4 and d_{13}), and the remaining six parameters are skin barrier-related parameters (k_1 , k_3 , b_2 , b_6 , d_1 , and d_3) that correspond to placebo effects and baseline severity of skin barrier defects rather than MoA of fezakinumab.

The two IL-22-related parameters (b_4 and d_{13}) can characterize responders for fezakinumab as virtual patients with lower d_{13} were more responsive to treatment by fezakinumab. The parameter, d_{13} , affect the IL-22 baseline level, and EASI-75 was slightly improved by stratifying virtual patients with a higher IL-22 baseline level (FIGURE S9). It is consistent with the results from actual clinical trials of fezakinumab, where a higher efficacy was observed in the AD patients with higher baseline mRNA levels of IL-22⁸⁸. The parameter, b_4 , describes the influence of IL-22 on skin barrier damage.

5.5. Influence of Th1 polarization on efficacy in rIFNg

Eight model parameters had a significant PRCC with the %improved EASI by rIFNg (FIGURE 4). One out of the nine parameters is strength of polarization for Th1 differentiation (k_9), which is related to IFNg (i.e., IFNg drives Th1 polarization), and the remaining seven parameters are skin barrier-related parameters (k_1 , k_3 , b_2 , b_4 , b_6 , d_1 , and d_3) that correspond to placebo effects and baseline severity of skin barrier defects rather than MoA of rIFNg. There was no improvement in EASI-75 by stratifying virtual patients with any cytokine baseline level (FIGURE S9).

6. Comparison of the parameter distributions between dupilumab good and poor responders

We compared distributions of the model parameters between good and poor responders for dupilumab based on the EASI-75 criterion (FIGURE S10), and confirmed that the ten parameters (k_1 , k_3 , k_{13} , k_{14} , b_2 , b_4 , b_6 , d_1 , d_3 , and d_{11}) that demonstrated a significant influence on %improve EASI of dupilumab (FIGURE 4) had different distributions for good and poor responders for dupilumab. Among the ten parameters, three parameters with larger PRCC (k_1 : -0.6, k_3 : 0.6, and b_2 : 0.6) with %improve EASI of dupilumab showed a larger difference in distributions between dupilumab good and poor responders, compared to the other seven parameters that has a smaller PRCC (k_{13} , k_{14} , b_4 , b_6 , d_1 , d_3 , and d_{11} : -0.2 ~ 0.3).

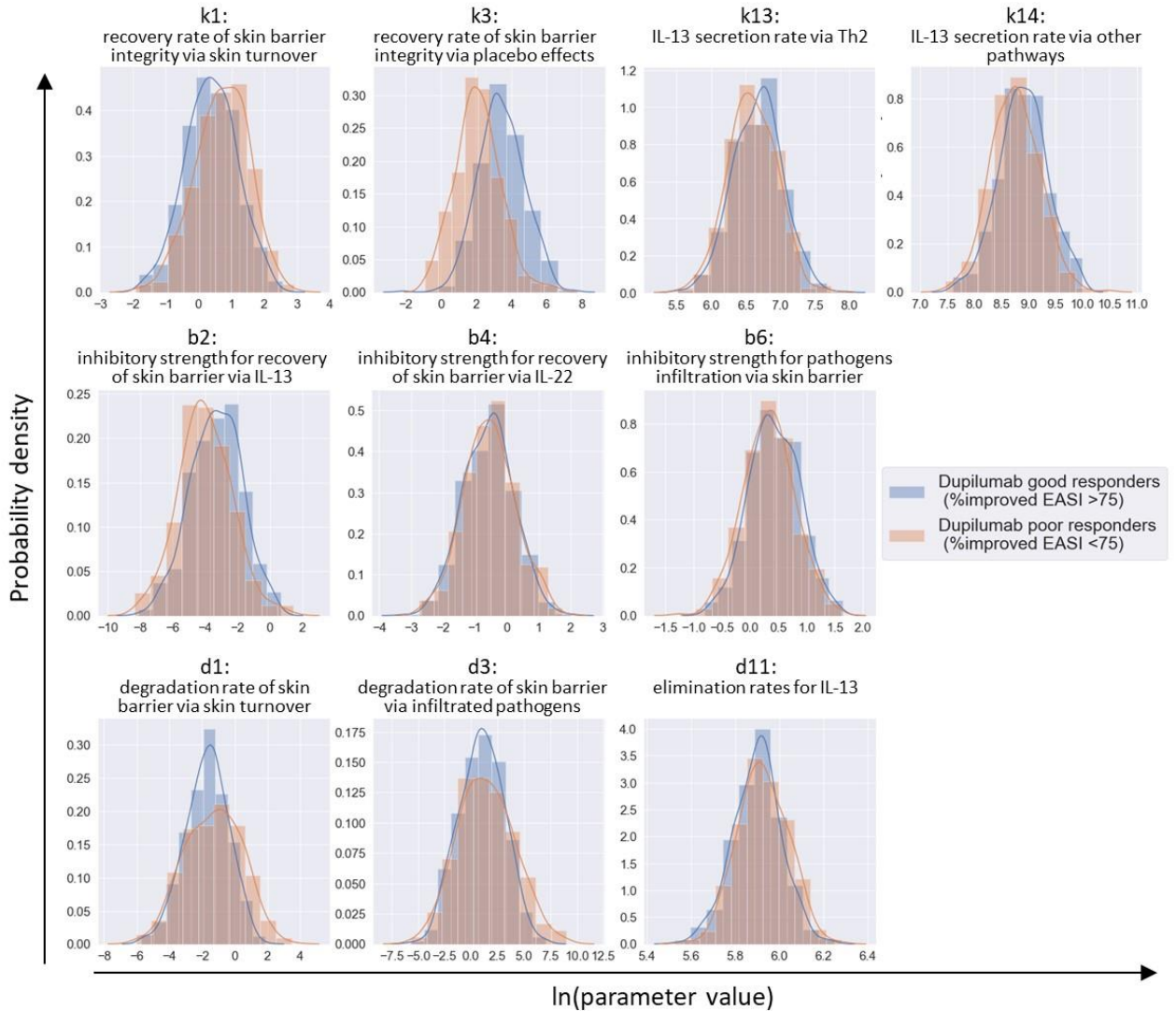


FIGURE S10 Distributions of model parameters for dupilumab good (blue) and poor (orange) responders.

The comparison visually confirmed that the 11 parameters (k_1 , k_3 , k_{13} , k_{14} , b_2 , b_4 , b_6 , d_1 , d_3 , and d_{11}) that had significant influence on %improve EASI of dupilumab (FIGURE 4) were differently distributed between dupilumab good and poor responders. We generated a large number of virtual patients (1000 virtual patients = 1000 sets of 52 parameter values) by randomly sampling each of the parameter values from the distribution in Eq. (3). The virtual patients were treated with dupilumab to simulate %improved EASI at 24 weeks and were categorized into dupilumab good responders (%improved EASI>75) or dupilumab poor responders (%improved EASI<75). Distributions of the 11 parameters were plotted for dupilumab good and poor responders separately.

7. References

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