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Biomarkers of therapeutic response to dupilumab in severe atopic dermatitis

Biomarkery odpowiedzi na leczenie dupilumabem w ciężkiej postaci atopowego zapalenia skóry

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Abstract

Atopic dermatitis is a chronic, heterogeneous inflammatory skin disorder affecting up to 20% of children and 2–10% of adults worldwide. In most patients, disease pathogenesis is driven by a type 2 immune response mediated by interleukin-4 and interleukin-13. Elevated type 2 biomarkers, including eosinophils, CCL17, and fractional exhaled nitric oxide, identify atopic dermatitis phenotypes that are highly dependent on these cytokines and responsive to their inhibition. Severe atopic dermatitis substantially impairs quality of life and, in a subset of patients, follows a treatment-refractory course associated with significant psychosocial burden. Dupilumab, a monoclonal antibody targeting the IL-4 receptor alpha, inhibits IL-4 and IL-13 signalling and represents a major therapeutic advance. Despite its proven efficacy and favourable safety profile, responses remain heterogeneous and difficult to predict. Consequently, the identification of reliable prognostic and predictive biomarkers has emerged as a key research priority. Advances in transcriptomics, proteomics, and metagenomics, combined with growing clinical evidence, support the development of integrated biomarker panels to guide personalised therapy. Clinical studies consistently demonstrate that dupilumab significantly reduces disease severity in many patients, underscoring the need for validated predictive markers. This review critically examines current evidence on biomarkers associated with atopic dermatitis pathophysiology and response to dupilumab, highlighting their predictive potential and relevance for routine clinical practice, and implications for precision medicine in the management of severe atopic dermatitis.

Keywords: dupilumab, severe atopic dermatitis, biomarkers, treatment

Streszczenie

Atopowe zapalenie skóry to przewlekła, zapalna dermatoza o wieloczynnikowej etiologii, dotykająca do 20% dzieci i 2–10% dorosłych na świecie. Choroba charakteryzuje się dużą heterogennością kliniczną i immunologiczną. U większości pacjentów dominującym mechanizmem jest odpowiedź typu 2, oparta na aktywacji szlaków IL-4 i IL-13. Podwyższone poziomy biomarkerów typu 2, takich jak eozynofile, FeNO czy CCL17, wskazują fenotypy szczególnie zależne od tych cytokin i dobrze reagujące na ich blokadę. Atopowe zapalenie skóry znacząco obniża jakość życia, a u części pacjentów przebiega ciężko i opornie na leczenie, niosąc duże obciążenie psychospołeczne. Postęp w transkryptomice, proteomice i metagenomice oraz rosnąca dostępność terapii celowanych podkreślają potrzebę identyfikacji biomarkerów umożliwiających personalizację leczenia. Przełomowym osiągnięciem w terapii atopowego zapalenia skóry ostatniej dekady jest dupilumab, przeciwciało monoklonalne blokujące IL-4Rα i hamujące sygnały IL-4 i IL-13. Choć jest ono skuteczne klinicznie i bezpieczne, odpowiedź na terapię bywa zmienna i trudna do przewidzenia. Identyfikacja biomarkerów prognostycznych i predykcyjnych, pozwalających przewidywać skuteczność dupilumabu w różnych fenotypach atopowego zapalenia skóry, stanowi obecnie

priorytet badawczy. Dynamiczny rozwój biologii systemowej oraz licznych badań klinicznych wskazuje na potrzebę kompleksowego przeglądu dostępnych biomarkerów zarówno już stosowanych, jak i obiecujących, lecz wymagających dalszej walidacji. Badania kliniczne wykazują, że leczenie dupilumabem znacząco redukuje ciężkość choroby u wielu pacjentów, co dodatkowo podkreśla znaczenie markerów predykcyjnych. Celem niniejszego przeglądu jest krytyczna analiza danych dotyczących biomarkerów atopowego zapalenia skóry oraz ich przydatności w przewidywaniu odpowiedzi na dupilumab w codziennej praktyce klinicznej.

Słowa kluczowe: dupilumab, ciężkie atopowe zapalenie skóry, biomarkery, leczenie

INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory dermatosis of multifactorial aetiology, affecting up to 20% of children and 2–10% of adults worldwide[1]. The disease exhibits substantial clinical and immunological heterogeneity. In most patients, AD is predominantly driven by a type 2 (Th2) immune response mediated through activation of the interleukin-4 (IL-4) and interleukin-13 (IL-13) pathways. Increased levels of type 2 inflammatory biomarkers, including eosinophils, fractional exhaled nitric oxide (FeNO), and CCL17, are associated with AD phenotypes that are highly dependent on these cytokines and tend to respond favourably to their inhibition[2]. AD markedly impairs quality of life and, in a subset of patients, follows a severe, treatment-refractory course associated with a considerable psychosocial burden. Advances in transcriptomic, proteomic, and metagenomic technologies, together with the expanding availability of targeted therapies, have highlighted the need for biomarkers that support personalised treatment approaches. One of the most important therapeutic advances in AD over the past decade has been the introduction of dupilumab**,** a monoclonal antibody targeting the IL-4 receptor alpha subunit (IL-4Rα), thereby inhibiting signalling mediated by both IL-4 and IL-13. Despite its proven clinical efficacy and favourable safety profile, response to dupilumab remains heterogeneous and difficult to predict. Consequently, the identification of prognostic and predictive biomarkers capable of anticipating therapeutic outcomes across different AD phenotypes has become a key research priority. In view of the rapid development of systems biology approaches and the growing body of clinical evidence, there is a clear need for a comprehensive synthesis of current knowledge on AD biomarkers, encompassing both those already implemented in clinical practice and those that remain promising yet insufficiently validated. Clinical studies consistently demonstrate that dupilumab therapy results in a significant reduction in disease severity in a substantial proportion of patients, further emphasising the importance of validated predictive markers[3,4]. The aim of the review is to critically appraise the available evidence on biomarkers associated with AD pathophysiology and response to dupilumab therapy, with particular emphasis on their predictive value in routine clinical practice.

METHODOLOGY

This article is a narrative review focusing on biomarkers associated with response to dupilumab therapy in patients with AD. A literature search was conducted using the PubMed, Scopus, and Google Scholar databases. The following keywords and their combinations were applied: "atopic dermatitis", "dupilumab", "biomarkers", "type 2 inflammation", "IL-4", "IL-13", "TARC", "CCL17", "CCL18", "IL-22", and "treatment response".
The search included articles published from 2017 through November 2025.

MECHANISM OF ACTION OF DUPILUMAB AND POTENTIAL BIOMARKER TARGETS

Dupilumab exerts its therapeutic effect through selective blockade of IL-4Rα, is the receptor subunit shared by the signalling pathways of the Th2 cytokines IL-4 and IL-13. As a fully human monoclonal IgG4 antibody, dupilumab inhibits the binding of IL-4 and the IL-13/IL-13Rα1 complex to IL-4Rα, thereby effectively suppressing signalling mediated by both cytokines. This dual inhibition interrupts key mechanisms of type 2 (T2) inflammation implicated in the pathogenesis of AD and other allergic diseases, including Th2 cell differentiation and activation of antigen-presenting cells[2]. Downstream, dupilumab inhibits phosphorylation of STAT6, a central transcriptional mediator of the IL-4/IL-13 axis, leading to broad normalisation of inflammatory molecular signatures in the skin[2,5].
The effects of dupilumab on Th2 cytokine pathways include reduced IL-5 production, resulting in decreased eosinophil activation and tissue migration. However, circulating eosinophil counts frequently remain unchanged during therapy[5]. In some patients, a transient increase in peripheral blood eosinophilia has been reported, likely reflecting impaired tissue migration and redistribution of eosinophils into the peripheral circulation. Importantly, this phenomenon does not diminish clinical efficacy and typically resolves over subsequent months of treatment. Moreover, emerging evidence suggests that higher baseline eosinophil counts may be associated with a more favourable treatment response in selected patient subsets[6].
Concomitantly, dupilumab modulates the expression of eosinophil- and lymphocyte-attracting chemokines, including eotaxins (CCL26) as well as CCL17 (TARC), CCL18

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(PARC), and CCL22. Reductions in these mediators correlate with decreased systemic and cutaneous inflammatory activity and with clinical improvement in AD[6,7].
In addition, dupilumab contributes to restoration of epidermal barrier function by inhibiting IL-4 and IL-13, cytokines known to suppress the expression of key structural proteins of the epidermis. Blockade of IL-4Rα also normalises the expression of other critical components of the epidermal barrier, improving the lipid and ceramide composition of the skin, as demonstrated in transcriptomic analyses and transepidermal water loss (TEWL) studies in patients treated with dupilumab[8–10].
Dupilumab therapy also exerts a beneficial effect on the skin microbiome, including a reduction in *Staphylococcus aureus* colonisation, which supports epidermal repair and reduces disease exacerbations. Treatment is associated with increased microbial diversity of the epidermis, restoring the cutaneous ecosystem towards a state resembling healthy skin, as confirmed in microbiome analyses[8–10].
From the perspective of predictive biomarkers, parameters reflecting activity of the IL-4/IL-13 axis appear to be of particular relevance. Baseline levels of these biomarkers correlate with the intensity of the type 2 inflammatory phenotype and may therefore predict both the magnitude and kinetics of the clinical response to IL-4Rα blockade.

Type 2 inflammatory markers

Type 2 inflammatory markers play a central role in the pathogenesis of AD, and many are directly regulated by the IL-4 and IL-13 cytokine pathways. By blocking IL-4Rα, dupilumab modulates the broader T2 inflammatory signalling network, resulting in reduced levels of chemokines, cytokines, and extracellular matrix-associated proteins. These molecular changes frequently correlate with clinical improvement in patients with a T2-high phenotype, as assessed using validated disease-severity scores such as EASI, IGA, or SCORAD[2,11,12].
Elevated baseline levels of type 2 inflammatory biomarkers have been associated with a greater reduction in inflammatory disease activity, with response rates reported in up to 75% of patients classified as responders[13]. A growing body of evidence indicates that several T2-associated biomarkers not only reflect disease activity and therapeutic efficacy but may also possess predictive value for treatment response to dupilumab[2,11].

TARC/CCL17

Thymus and activation-regulated chemokine (TARC/CCL17) is a Th2-associated chemokine produced by dendritic cells and keratinocytes in AD. By binding to the CCR4 receptor, it promotes the recruitment of Th2 lymphocytes into the skin. Both serum and tissue levels of TARC represent some of the most extensively validated biomarkers of AD activity, typically increasing with inflammatory severity and decreasing significantly following initiation of effective therapy.
In clinical studies, dupilumab treatment has been associated with reductions in TARC levels exceeding 50% after 16 weeks, depending on the study population and analytical method. Across multiple analyses, decreases in TARC consistently correlate with improvements in EASI and SCORAD scores, supporting its utility as a marker of biological treatment response.
However, TARC is not specific to AD, as elevated levels are also observed in other atopic diseases. Consequently, its predictive value requires interpretation within a broader immunological context rather than as a standalone biomarker[2,5,14,15].

PARC/CCL18

Pulmonary and activation-regulated chemokine (PARC/CCL18) is an IL-4/IL-13-induced chemokine produced primarily by macrophages and dendritic cells, including Langerhans cells. It is overexpressed in both the skin and serum of patients with AD. Dupilumab significantly reduces PARC expression in the skin, as demonstrated by transcriptomic analyses of biopsy specimens and tape-strip samples, and also lowers serum concentrations, although the magnitude of these changes appears more variable across studies and populations compared with TARC.
Available data indicate that decreases in CCL18 frequently accompany clinical improvement and restoration of epidermal barrier parameters. However, validated cut-off values predictive of sustained remission are currently lacking[2,5,16,17].

IL-13

Interleukin-13 is a key type 2 cytokine that impairs keratinocyte differentiation and promotes chemokine production in AD. Blockade of IL-4Rα with dupilumab results in a marked reduction of IL-13 expression in the skin, as shown by transcriptomic and immunohistochemical analyses, leading to partial normalisation of the inflammatory transcriptome.
Several studies suggest that higher baseline cutaneous IL-13 expression may be associated with a more favourable clinical response to dupilumab, supporting its role as a potential predictive biomarker[2,5,13,18].

IL-4Rα

Expression of IL-4Rα is increased on keratinocytes and immune cells in the skin of patients with AD, resulting in enhanced activation of the JAK–STAT6 pathway and sustained type 2 inflammation. Transcriptomic studies have demonstrated that dupilumab effectively suppresses IL-4/IL-13 signalling, reflected by significant downregulation of STAT6-induced genes and partial normalisation of the cutaneous inflammatory profile.
Across multiple analyses, higher baseline transcriptomic activity of type 2 pathways, including IL-4Rα-related signatures, has been associated with improved clinical response to dupilumab[7,13].

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Periostin

Periostin is an IL-13-induced extracellular matrix protein involved in skin remodelling and fibrotic processes and is frequently elevated in patients with AD. Clinical studies have demonstrated significant reductions in periostin levels in both serum and tissue during dupilumab therapy, reflecting modulation of IL-4/IL-13-driven inflammation.
Although the magnitude of periostin reduction varies across studies, available clinical data are encouraging and suggest an association with changes in skin remodelling, including alterations in skin thickness, vascular patterns, and reductions in oedema and inflammatory infiltrates, as assessed by ultrasound imaging and histological analysis[13,19–22].

IgE

Total immunoglobulin E (tIgE) represents a classical marker of type 2 inflammation and allergic disease. In many patients with AD, tIgE levels are markedly elevated, although values vary substantially between individuals and do not consistently correlate with disease severity. Dupilumab induces a gradual reduction in tIgE levels, often by several tens of percent over months of treatment, as demonstrated in phase II and III clinical trials[23–26].
Despite its limited value as a short-term predictive marker, tIgE may reflect long-term modulation of type 2 immune activity.

Eotaxin-3 (CCL26)

Eotaxin-3 (CCL26) is a CCR3-binding chemokine with strong eosinophil chemotactic properties. In humans, it is produced by keratinocytes and endothelial cells in response to type 2 cytokines, particularly IL-4 and IL-13, via STAT6-dependent signalling, underscoring its role as a marker of Th2 axis activation in both skin and peripheral blood[27–30].
Because dupilumab blocks IL-4Rα and suppresses IL-4/IL-13 signalling, reductions in CCL26 represent an expected and consistently observed therapeutic effect, primarily documented in observational and transcriptomic studies[29].
Elevated baseline CCL26 levels may indicate pronounced Th2 activity and have been associated with favourable responses to IL-4/IL-13 blockade[28,29,31].
CCL26 appears to be a promising monitoring biomarker and correlates with EASI scores; however, its prognostic utility requires confirmation in larger prospective analyses[28].

IL-31

Interleukin-31 is produced mainly by Th2 lymphocytes and mast cells and is recognised as a key mediator of pruritus in AD due to its effects on sensory neurons and keratinocytes. IL-31 levels correlate with itch intensity and intraepidermal nerve fibre density[32,33].
Clinically, dupilumab rapidly reduces pruritus in most treated patients. However, data regarding its effect on serum IL-31 concentrations remain inconsistent, likely reflecting the predominantly local activity of IL-31 within the skin and peripheral nerve endings. As a result, circulating levels may not accurately capture tissue-level cytokine activity[32,34].

IL-22

Interleukin-22, primarily derived from Th22 and Th17 cells, acts on keratinocytes to promote proliferation, impair differentiation, and modulate antimicrobial peptide expression. IL-22 has been linked to lichenification and chronic plaque-like lesions characteristic of certain AD subtypes[35].
Evidence suggests that in patients with a dominant IL-22-driven inflammatory signature, clinical response to isolated IL-4/IL-13 blockade with dupilumab may be attenuated, reflecting the contribution of non-IL-4/IL-13 pathways. Accordingly, IL-22 may be more useful for identifying patients who could benefit from IL-22-targeted therapies (e.g. fezakinumab) or combination strategies[18,28,36].

Eosinophil-related biomarkers

Eosinophils are key effector leukocytes of the immune system and an integral component of type 2 immune responses, atopic diseases, and hypersensitivity reactions. They originate in the bone marrow under the influence of IL-5, IL-3, and granulocyte–macrophage colony-stimulating factor (GM-CSF), with IL-5 representing the principal differentiation factor. Following maturation, eosinophils migrate into peripheral blood and subsequently infiltrate inflamed tissues, including the skin in AD, under the influence of chemokines such as CCL11 (eotaxin-1), CCL24 (eotaxin-2), and CCL26 (eotaxin-3)[37,38]. Their surface expression of CCR3 confers high sensitivity to eotaxins and facilitates tissue recruitment[39].
Upon activation in the skin by IL-4, IL-5, and IL-13, eosinophils release cytotoxic granule proteins, including major basic protein (MBP), eosinophil cationic protein (ECP), eosinophil-derived neurotoxin (EDN), and eosinophil peroxidase (EPO). These mediators contribute to keratinocyte damage, intensification of pruritus, persistence of inflammatory processes, and tissue remodelling. In addition, eosinophils actively produce leukotrienes, cytokines, growth factors, and reactive oxygen species, promoting epidermal barrier disruption and facilitating *Staphylococcus aureus* colonisation. In AD, increased eosinophil infiltration in the skin and elevated peripheral blood eosinophil counts correlate with disease severity.
Blockade of IL-4/IL-13 signalling with dupilumab suppresses type 2 inflammatory pathways, reducing eotaxin expression in the skin and improving epidermal barrier function[40,41]. Consequently, eosinophils represent an important component of AD pathophysiology and a potential biomarker of treatment response. However, dynamic changes in eosinophil counts during therapy require careful clinical interpretation.

Lactate dehydrogenase (LDH)

Lactate dehydrogenase (LDH) is a nonspecific marker of tissue damage, anaerobic metabolism, and inflammatory activity. In AD, elevated LDH levels may reflect

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keratinocyte apoptosis, epidermal barrier disruption, and localised hypoxia associated with inflammatory infiltrates[42]. Observational data suggest that baseline LDH concentrations correlate with disease severity and may be linked to more difficult disease control, particularly in patients with high type 2 inflammatory activity, chronic disease phenotypes, and lichenification.

In the context of dupilumab therapy, elevated pretreatment LDH levels have been proposed as a potential indicator of a phenotype less likely to achieve complete remission, although available data remain heterogeneous. Several studies indicate that LDH may decrease during effective dupilumab treatment in parallel with clinical improvement, correlating with reductions in EASI scores at 3, 6, and 9 months of therapy[43]. Thus, LDH may serve as an adjunctive biomarker for monitoring treatment response, while its limited specificity should be acknowledged[3,25,43].

SKIN MICROBIOME AS A BIOMARKER IN ATOPIC DERMATITIS

The skin of patients with AD is characterised by profound microbial dysbiosis, most notably overrepresentation of *Staphylococcus aureus* and reduced microbial diversity[44]. During disease flares, *S. aureus* abundance may increase markedly relative to other components of the cutaneous microbiota, promoting inflammatory responses[45–47].

Dupilumab induces substantial normalisation of the epidermal barrier through inhibition of IL-4/IL-13 signalling, improved keratinocyte differentiation, elongation of ceramide chains with restoration of lipid barrier integrity, and increased hydration of the stratum corneum[9,10,48]. These effects are associated with reduced *S. aureus* colonisation, increased bacterial diversity, and restoration of commensal taxa, including *Cutibacterium* spp. and *Corynebacterium* spp.[9,46].

Normalisation of the skin microbiome correlates with clinical improvement, rendering microbiome-related parameters a promising, although still exploratory, biomarker of response to dupilumab therapy.

PHENOTYPES ASSOCIATED WITH REDUCED RESPONSE TO DUPILUMAB

Despite high overall efficacy, a subset of patients fails to achieve satisfactory clinical response. RNA sequencing studies indicate that patients with dominant IL-22-driven inflammation or enhanced Th17-related gene expression may exhibit attenuated clinical improvement following isolated IL-4/IL-13 blockade[36].

Furthermore, disease phenotypes characterised by elevated baseline LDH and C-reactive protein levels, together with pronounced keratinocyte activation, may reflect more entrenched inflammatory states in which IL-4/IL-13 is not the sole pathogenic axis[6,43]. In addition, patients with heavy *S. aureus* colonisation, recurrent secondary infections, or toxin-producing strains may respond more slowly to dupilumab and may require concomitant antibacterial or antiseptic interventions to optimise therapeutic outcomes[6,9].

SUMMARY

Dupilumab is a highly effective and generally safe biologic therapy for moderate-to-severe AD. It selectively blocks IL-4Rα, inhibiting IL-4 and IL-13 signalling and modulating type 2 immune responses. This mechanism suppresses Th2 lymphocyte activation, reduces pro-inflammatory cytokine and chemokine production, restores skin barrier function, and contributes to normalisation of the skin microbiome.

Key biomarkers of type 2 inflammation – including TARC/CCL17, PARC/CCL18, IL-13, IL-31, periostin, IgE, and eosinophils – correlate with disease severity and clinical outcomes. Their reduction during treatment often parallels improvements in EASI, SCORAD, and IGA scores. Microbiome-related parameters, such as *Staphylococcus aureus* colonisation and bacterial diversity, also reflect disease activity and therapeutic response, making them promising monitoring and potential predictive markers. However, further validation is required. Notably, therapeutic responses may also vary across patients with distinct molecular phenotypes of AD.

CONCLUSIONS

No single biomarker reliably predicts clinical response. Integrated biomarker panels combining immunological, transcriptomic, and microbiological data, together with clinical assessment, offer the greatest potential for personalised therapy.

Prospective studies are urgently needed to validate predictive and monitoring biomarkers for dupilumab. Such research will clarify mechanisms of response, refine efficacy predictions, and support evidence-based clinical decision-making, ultimately improving treatment safety and effectiveness in routine practice.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organisations which might negatively affect the content of this publication and/or claim authorship rights to this publication.

Author contribution

Original concept of study: KK. Collection, recording and/or compilation of data: MB. Analysis and interpretation of data: KK, JH. Writing of manuscript: KK, MB, JH. Critical review of manuscript; final approval of manuscript: AT, BK.

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