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Role of Biomarker and Personalized Medicine in Atopic Dermatitis Management

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Abstract Atopic dermatitis (AD) is closely related to the immunological disorder. One of the main therapeutic strategies for atopic dermatitis is to control the immune system. Many biomarkers were identified to have some role in atopic dermatitis progression. Disease biomarkers are important and helpful in the treatment of atopic dermatitis. Biomarkers may identify the best-personalized treatment option for atopic dermatitis management which is known as personalized medicine. Here, we discuss some biomarkers that may relate to a treatment option for atopic dermatitis in different conditions and different patients. Biomarker profile differences in some people may correlate to a different treatment option. Here we discuss the best treatment option for atopic dermatitis based on biomarkers. This study design as a review and was conducted following PRISMA guidelines. Publications were searched in PubMed. 15 studies related to AD biomarkers were found that met the inclusion criteria. Th1 (CXCL9), Th2 (IL-13, CCL17/CCL22), Th17/Th22, IgE and epidermal thickness change significantly in clinical trial treatments. Biomarkers play role as severity assessment and personalized medicine.

Keywords Atopic dermatitis, Biomarker, Personalized medicine, Management

1. Introduction

The prevalence of AD is estimated to be 15-20% in children and 1-3% in adults, and the incidence has increased by 2 to 3 fold during the past decades in industrialized countries [1]. Atopic dermatitis (AD) is caused by a complex interaction of immune dysregulation, epidermal gene mutations, and environmental factors that disrupts the epidermis causing intensely pruritic skin lesions. Repeated scratching triggers a self-perpetuating itch-scratch cycle, which can have a significant impact on the patient's quality of life [2]. In a review of cohort studies, 38% of adults with AD had symptom onset in childhood. Many describe pain, stinging and embarrasing from their AD impacting their choice of clothing. The burden increases with increasing severity of disease [3]. The diagnose tool that use widely worldwide is Hanif and Rajka's criteria that based on clinical appearance. The severity of AD also identified by tools based clinical appearance, such as SCORing of Atopic Dermatitis (SCORAD), Eczema Area and Severity Index (EASI) and Investigator's Global Assessment (IGA) that's rely on the observer's subjective assessment [4] But it is also known that in the AD patient's skin lesions there is found infiltration of T-helper type 2 (Th2) cells and increased dendritic cells. Dendritic cells induce cytotoxins that activate eosinophils, and Natural Killer (NK) cells [5]. In addition, Th2 cells produce various pro-inflammatory cytokines, including Interleukin (IL)-4, IL-5, and IL-13. IL-4 induced the production of immunoglobulin (Ig) E to develop hypersensitivity reaction [6]. It is clear that the pathogenesis of AD is not only associated with Th2 but also Th1 and Th17. The heterogeneity of Th22 cytokine it is unlikely that novel molecular therapies targeting specific immunologic pathways will be equally effective in all patients with AD, which makes stratification of subtypes of patients with AD of increasingly important [7]. The specific pathway of immunological mechanism in AD lead many study to found specific biomarker. Some biomarkers may relate to a treatment option for atopic dermatitis in different conditions and different patients.

2. Method

This study design as a review and was conducted following PRISMA guidelines. Publications were searched in PubMed. The following inclusion criteria of the articles were: (a) Articles published in 2017 until 22 September 2022; (b) Keyword used "atopic dermatitis biomarker"; (c) Publication defined as Clinical trials; (d) Publication defined as a Free-full text article; (e) Publication correlate with diagnosis and management of atopic dermatitis disease; (f) English language. Additionally, we conducted a manual search in the references to search the meaning or terms that used in publication.

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3. Biomarkers to Diagnostic in DA

Biomarker comes from the word "biological marker" which means a broad subcategory of medical signs that can be measured objectively. Biomarker difference from clinical signs and could play a significant role in the diagnosis, prognosis and management of AD. WHO defined biomarker as "any substance, structure or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease. Biomarkers; can be classified into markers of exposure, effect, and susceptibility" [4]. The biologic origin of a biomarker could be genomic information, transcriptomic profiles obtained by analysis of mRNA and miRNA, proteins such as cytokines and other mediators from body fluids (whole blood, serum, plasma, tissue fluids) or tape stripping, and morphological information [8].

The elevated of serum IL-19 level is known relevance in AD and psoriasis severity [9]. In a cohort study involving Asians, African-American and Caucasians, serum IgE levels were elevated in All Asian patients (>480ng/ml) while among Caucasian and African-American patients the relative distribution for elevated IgE levels was 80%. Asian patients were predominately associated with the low inflammatory subgroup, whereas African-American associated with the high inflammatory subgroup, and Caucasian distributed evenly. There is association to baseline EASI Score, SCORAD Index, Itch Numeric Rating Scale (NRS) and Dermatology Life Quality Index (DLQI). Specifically, the high inflammatory subgroup was associated with higher disease score as compared to the low inflammatory subgroup. The study also found that Th2/Th22-related biomarkers, including IL-13, IL-22, Thymus and activation-regulated chemokine (TARC)/CCL17, Macrophage-derived chemokine (MDC)/CCL22, Monocyte chemo-attractant protein (MCP)-4/CCL13 and MCP-3/CCL17 correlate with disease severity. Furthermore IL-13, MCP-3 and TNFβ were found to be variable in both high inflammatory and low inflammatory subgroup and can be potential biomarker to detect severity of AD [10].

With the skin tape strip (STS) method, IL4R, CCL22, CCR4 also found correlate with severity of AD [11]. In European-Caucasian patients, a study using skin tape strip found that concentration of inflammatory cytokine in stratum corneum such as IL-18 CCL17, TARC/CCL17, MDC/CCL22, Cutaneous T-cell attracting chemokine (CTACK)/CCL27, IL-8/CXCL8 are high significantly in AD with skin lesions rather than in AD non lesions [12] Another study that using skin tape strip, found a group with 45 proteins as principal component 1 (PCI1) highest in AD with food allergy (FA). It has correlation with elevated trans-epidermal water loss (TEWL), specifically serine protease inhibitors b12 (SERPINB12) and gelsolin (GSN). 45 PCI1 proteins also significantly high in AD with FA rather than AD without FA and lowest in control group [13]. Studies found that there is characteristics in AD sample both blood or skin and can be identify the severity of AD (**Table 1**).

Treatments for AD based on Biomarker and Personalized Medicine:

Study found that Th2 cytokines play a key role in allergic disorders, include AD. Specifically; IL-4 and IL-13 and the heterodimeric IL-4 receptor (IL-4R). That's way the potential treatment of AD may correlate with that markers. Dupilumab is a humanized IgG4 monoclonal antibody that targets the IL-4 receptor alpha chain (IL-4Rα) complex. The potential mechanism of action of Dupilumab in targeting the IL-4R complex is may inhibit IL-4 binding to IL-4Rα, inhibit the recruitment of γc to IL-4Rα chain, and inhibit the recruitment of the IL-R4α to IL-13Rα1. Dupilumab has been approved by the food and drug administration (FDA) in the United States for the treatment of moderate-to-severe atopic dermatitis in uncontrolled patients [14]. In a clinical trial, Dupilumab significantly reduce the inflammatory markers by inhibit the IL-4Rα rather than the placebo treatment. The biomarkers that notably the type 2 chemokines such as CCL17, CCL18 and the periostin after 16 week of treatment. TARC and pulmonary and activation-regulated chemokine (PARC) decrease and higher microbial diversity is correlate with the staphylococcus aureus colonization [15-16]. Tralokinumab, a fully human monoclonal antibody, specifically neutralizes IL-13, a key cytokine driving peripheral inflammation in AD. Its known to reduce daily pruritus through NRS [17]. Tralokinumab 300mg proven affect the clinical severity of AD through SCORAD index and Itchy NRS, the biomarker that found decrease with the severity is TARC, PARC and serum IgE, reversely dipeptidyl peptidase-4 (DPP-4) which the protein biomarker-induced by IL-13, increase in patients without Tralokinumab 300mg treatment [18].

OX40 is one of the co-stimulatory molecules expressed on T cells, and it is engaged by OX40L, primarily expressed on professional antigen-presenting cells such as dendritic cells [19]. GBR 830 is a humanized mAb against OX40. The clinical study found that the GBR 830 treatment with dose 10mg/kg can reduce significantly the clinical sign through Itchy NRS in patients with moderate to severe AD [20].

Tezepelumab is fully human monoclonal antibody that binds to thymic stromal lymphopoietin (TSLP), thereby preventing its reaction to TSLP receptor complex. TSLP is a innate cytokine that activates dendritic cells (DC) [21]. Tezepelumab 280 mg subcutan every 2 weeks with the class 3 topical corticosteroids (TCS) can reduce the clinical symptom of AD and reduce biomarkers such as IgE and DPP-4 that are high in AD with TCS treatment. The other biomarkers found was serum Periostin, and TARC/CCL17 which already low with TCS treatment, and being lower with Tezepelumab treatment although not significantly [22]. Crisaborole ointment 2% is a nonsteroidal phosphodiesterase 4 inhibitor for the treatment of mild to moderate AD. Inhibition of phosphodiesterase 4 by Crisaborole increase levels pf 3'4'-cyclic adenosine monophosphate in inflammatory cells, leading to activation of nuclear factor κB

and nuclear factor of activated T-cell lead pathways and subsequent suppression of inflammatory cytokine release [23]. Crisaborole ointment 2% induced significant changes compared with vehicle in several pathogenic processes associated with AD, including IL-13, Interferon (IFN)γ, IL-22, IL-1 and/or TNF, T-cell and DC genes and Th17/th22 [24].

Phosphodiesterase-4 (PDE4), mainly present in immune cells, epithelial cells and brain cells, manifest as an intracellular non receptor enzyme that modulates inflammation and epithelial intact. Inhibition of PDE4 is predicted to have diverse effect via the elevation of the level of cyclic adenosine monophosphate (cAMP) and the subsequent regulation of a wide array of genes and proteins [25]. Apremilast is an oral PDE-4 inhibitor, approved for use in the management of psoriasis and psoriatic arthritis as well AD [26]. Apremilast 40 mg (APR40) give to patients with moderate – severe AD twice a daily and its improved the clinical symptom through EASI score significantly than apremilast 30 mg (APR30) and more from placebo. APR40 also significantly reduce the biomarkers, epidermal hyperplasia and inflammatory marker associated with Th17/Th22 pathways [27].

Study found that the symbiotic mixture intervention in infants with high IgE-associated AD can improvement significantly the SCORAD score than in the placebo, but not significant in infant with no appearance of IgE-associated AD. The symbiotic mixture is hydrolysed formula with *Bifidobacterium breve* M-16V and galacto-/fructooligosaccharide mixture [28]. Recent clinical trial study also did intervention with the symbiotic mixture of prebiotic short-chain galacto-oligosaccharides (scGOS), long-chain fructo-oligosaccharides (lcFOS), and a probiotic strain *Bifidobacterium breve* M-16V together with class 7 TCS treatment in infants with IgE-associated AD. After 4 month dietary intervention, SCORAD index improved with Th2/Th1 chemokine ratios for CCL17/CXCL9, CCL22/CXCL9, CCL20/CXCL10 and CCL20/CXCL11 was detected associated with the active intervention after 4 month dietary [29].

Gusacitinib (ASN002) is an oral dual inhibitor of (Janus kinase) JAK and tyrosine-protein kinase spleen tyrosine kinase (SYK) [30]. In a clinical trial study, ASN002 is given in three dose of 20 mg, 40 mg and 80 mg. There is significant improvement in EASI score and decreasing biomarkers (Th1, Th2 and Th17/Th22) after the treatment of 40 mg and 80 mg ASN002 [31].

The TCS treatment was broadly use worldwide in a decade and known to be effective as anti-inflammatory drugs. A study order the potency of TCS including pimecrolimus, betamethasone dipropionate, and clobetasol propionate versus emollient as a vehicle to moderate-severe AD patients. Betamethasone dipropionate, and clobetasol propionate significantly improved the clinical symptom through total sign score (TSSs), TEWL level, tissue biomarkers (Th1, Th2 and Th17/Th22), and epidermal hyperplasia rather pimecrolimus, same as vehicle that has no significant improvement [32]. The role of biomarker in management of AD recently developed across many study (**Table 2**).

From 2017 to September 2022, many clinical trial studies of AD biomarkers were published. In PubMed search, 15 studies related to AD biomarkers were found that met the inclusion criteria. Most visible in these 15 studies was the role of biomarkers in the objective assessment of AD severity and drug efficacy in both adult patients and dietary interventions in infants. The Th1 chemokines (CXCL9), Th2 (IL-13, CCL17/CCL22) and Th17/Th22 appeared to be significantly decreased which was consistent with the improvement of clinical symptoms. IgE and epidermal thickness are also often used as biomarkers to assess drug effectiveness.

Table 1. Characteristics and Severity of Atopic Dermatitis

Sample	Participants	AD severity	Group	Biomarker result	Reference
Blood	124 patients	Moderate – severe AD	AD treatment with topical cortico-steroid and AD with placebo	IL-19 correlate with AD severity	Konrad, et al. 2019 (9)
Peripheral blood	123 patients, 20 control (Asian, American Africa, Caucasian)	Moderate – severe AD	High inflammatory, Low inflammatory and control	TNFβ, MCP‐3 and IL‐13 correlate with the severity of AD	Sims, et al 2021 (10)
Skin (STS method)	30 patients, 25 control (Caucasian)	Mild – severe AD	Lesional, Non lesional skin and control	IL13, IL4R, CCL22, CCR4 correlate with severity of AD	Dyjack, et al. 2018 (11)
Stratum corneum (STS method)	15 patiens, 16 control (European-Caucasian)	Mild – severe AD	Lesional, Non lesional skin and control	IL-18 CCL17, TARC/CCL17, MDC/CCL22, CTACK/CCL27, IL-8/CXCL8 is high significantly in AD with skin lesions	Clausen, et al. 2020 (12)
Skin (STS method)	137 patients (Caucasian, African-American)	Mild – moderate AD	AD with FA, D without FA, control	45 PCI1 proteins high in AD with FA and can predict TEWL	Goleva, et al. 2020 (13)

Table 2. The role of biomarker in management of Atopic Dermatitis

Treatment	Sample	AD Severity	Results	Biomarkers	Refferences
Dupilumab (loading dose 400mg in day 1, followed by 200 mg every week)	Skin biopsy and blood specimens of 26 patients receive dupilumab and 25 patients receive placebo (Lesional and non lesional skin)	Moderate – severe AD	Dupilumab significantly suppressed mRNA expression of genes of type 2 inflammation regulated by IL-4Rα-mediated. At week 16 Dupilumab reduce type 2 -polarizing chemokines MCP-4/CCL13, PARC/CCL18, Eotaxin-3/CCL26, TARC/CCL17, MDC/CCL22. Reduce IL 13 and IL31.	Dupilumab reduce circulating serum concentration of CCL17, CCL18 and periostin from baseline through 16 week and reduce IgE	Guttman-Yassky, et al. 2019 (15)
Dupilumab (loading dose 400mg in day 1, followed by 200 mg every week)	DNA Swab and blood specimens of 26 patients receive dupilumab and 25 patients receive placebo (Lesional and non lesional skin)	Moderate – severe AD	Staphylococcus bacterial decrease in week 4 until week 16 of observation, in all groups and mainly significant in the dupilumab-treated patients in lesional skin	TARC and PARC decrease is correlating with the decreased of S. aureus. Higher microbial α-diversity is associated with the decreasing of S. aureus	Callewaert, et al. 2020 (16)
Tralokinumab	Blood specimens of 204 patients (51 placebo, 50 with 45mg Tralokinumab, 51 with 150mg Tralokinumab, 52 with 300mg Tralokinumab	Moderate – severe AD	Participants treated with 300mg of Tralokinumab demonstrated improvements in SCORAD, DLQI, and itchy NRS versus placebo	Serum periostin, TARC/CCL17, and IgE decrease in patient with Tralokinumab treatment at week 12. And DPP-4 increase in placebo participants at week 12.	Wollenberg, et al. 2019 (18)
GBR 830 (10mg/kg)	Skin biopsy and blood specimens of 20 patients with GBR 830 and 3 patients placebo	Moderate – severe AD	GBR 830 significantly reduce Th1 cytokines, Th2, and Th17/Th22.	$OX40^+$ T cells, $OX40L^+$ dendritic cells and hyperplasia thickness found significantly reduce	Guttman-Yassky, et al. 2019 (20)
Tezepelumab (s.c. 280 mg/ placebo every 2 weeks + class 3 TCS)	Blood specimens of 113 patients with treatment and 111 patients placebo	Moderate – severe AD	Tezepelumab + class 3 TCS reduce the clinical severity	DDP-4, IgE, periostin serum and TARC/CCL17 reduces with TCS treatment but lower with the addition of Tezepelumab treatment	Simpson, et al. 2019 (22)
Crisaborole ointment 2%	Skin biopsy and blood specimens of 38 patient AD treat with Crisaborole or vehicle. (Lesional and non lesional)	Mild to moderate AD	Early improvement (24 hours) in pruritus NRS after the treatment of Crisaborole versus vehicle.	The thickness of epidermal hyperplasia, Th2, Th17/Th22 significantly reduces after day 15 treatment of Crisaborole	Bissonnette, et al. 2019 (24)
Apremilast	Skin biopsy and blood specimens of 146 patients (placebo, APR30, APR40)	Moderate – severe AD	At week 12, patient eith APR40 treatment showed significantly improvement in clinical score based on EASI score, APR30's also has improvement, but not significant.	Reduction in epidermal hyperplasia and inflammatory marker associated with Th17/Th22 pathways.	Simpson, et al. 2019 (27)
Dietary intervention (hydrolyzed whey based infant formula with or without 90% scGOS, 10% lcFOS, and B. breve M-16V at a dose of $1.0x10^8$ cfu/g) + class 7 TCS	Skin biopsy and blood specimens of 31 infants up to 11 months of age (16 active group, 15 control group)	Moderate – severe AD	SCORAD index improvement after 4 month dietary intervension	Th2/Th1 chemokine ratios for CCL17/CXCL9, CCL22/CXCL9, CCL20/CXCL10 and CCL20/CXCL11 was detected associated with the active intervention after 4 month dietary intervention.	Hulshof, et al. (29)

Treatment	Sample	AD Severity	Results	Biomarkers	Refferences
ASN002 (20mg, 40mg and 80mg)	Blood specimens of 36 patients	Moderate – severe AD	EASI score improvement significant with ASN002 dose 40 mg and 80mg, but not with 20mg at day 28	Th1, Th2 and Th17/Th22 decreased with the treatment of ASN002 40 and 80 mg	Bissonette, et al. 2019 (31)
Topical treatments of Pimecrolimus, betamethasone dipropionate, Clobetasol propionate, and emollient (as vehicle)	Skin biopsy of 30 patients	Mild to moderate AD	betamethasone dipropionate and Clobetasol propionate showed significant clinical improvement over vehicle through TSSs, TAA scores and TEWL levels at day 8 and day 15	Epidermal hyperplasia thickness in lesional skin reduce after TCS treatment close to non lesional level. Th1, Th2 and Th17/Th22 improvement with TCS but not Pimecrolimus and vehicle	Guttman-Yassky, et al. 2017 (32)

In the management of AD, biomarkers also play role to be a part of personalized medicine. In infant patients who suffers moderate – severe DA, biomarkers help to breakdown that dietary intervention only improved in infant with IgE-associated AD. In Dupilumab treatment of moderate to severe AD, study also found that the decrease of S. aureus only found in lesional skin, but not in non lesional skin.

4. Conclusions

In AD, clinical symptom assessment such as SCORAD index, EASI score, pruritus NRS, widely used worldwide. But the assessment is subjective. Biomarkers in AD play important role as objective assessment. Biomarkers also can help to breakdown the best personalized medicine for DA. It is still necessary to study the role of biomarkers to detect the safety and possibility of appropriate therapy in several conditions.

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