


Current Updates on Moderate to Severe Atopic Dermatitis Management: From Pathogenesis to Breakthrough Treatment

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ABSTRACT

Atopic dermatitis (AD), characterized by recurrent eczematous lesions and pruritus, is a major contributor to the total global burden of disability. The common management practice includes patient education and topical emollients and is heavily reliant on the use of anti-inflammatory agents with systemic corticosteroids. Monoclonal antibodies provide a novel, targeted approach towards specific cytokines. This study aims to highlight the novel systemic therapeutic drug aimed at specific targets. A comprehensive literature review utilizes databases including EMBASE, EBSCOhost, PubMed, Scopus, and Wiley Online Library, using keywords: "monoclonal antibody" AND "therapy" AND "atopic dermatitis". Relevant papers containing different updates in atopic dermatitis management and the utilization of monoclonal antibodies are included in this review. The current regimen of monoclonal antibodies offers better management of moderate-to-severe AD. Monoclonal antibodies have become a promising therapy as they demonstrate better therapeutic effects in terms of skin barrier protection and anti-inflammatory and pruritus-reducing effects. However, its application still faces various challenges such as side effects and infections. The heterogeneity and relapsing nature also add to the complexity and risk profile of AD management.

Keywords: Atopic dermatitis, monoclonal antibody, therapy.

ABSTRAK

Dermatitis atopik (DA), kondisi yang ditandai dengan lesi eksim berulang dan pruritus, merupakan kontributor utama beban kecacatan global. Praktik penatalaksanaan yang umum mencakup edukasi pasien dan emolien topikal serta agen antiinflamasi *corticosteroid* sistemik. Antibodi monoklonal merupakan suatu pendekatan tata laksana baru dan mampu menarget sitokin spesifik. Penelitian ini bertujuan menyoroti obat sistemik baru untuk target spesifik seperti antibodi monoklonal. Tinjauan literatur komprehensif menggunakan *database* EMBASE, EBSCOhost, PubMed, Scopus, dan Wiley Online Library, dengan kata kunci: "antibodi monoklonal" DAN "terapi" DAN "dermatitis atopik". Penelitian relevan berisi pembaruan pengelolaan DA dan penggunaan antibodi monoklonal disertakan dalam tinjauan ini. Antibodi monoklonal yang telah dikembangkan hingga saat ini menawarkan penatalaksanaan DA sedang hingga berat yang lebih baik. Namun, penerapannya masih menghadapi berbagai tantangan seperti efek samping dan risiko infeksi. Heterogenitas dan sifat kekambuhan juga menambah kompleksitas dan profil risiko pengelolaan DA. **Muhammad Alifian Remifta Putra, Vincent Kharisma Wangsaputra, Raya Makarim Penantian. Tata Laksana Terkini Dermatitis Atopik Sedang dan Berat: Dari Patogenesis hingga Terobosan Tata Laksana.**

Keywords: Dermatitis atopik, antibodi monoklonal, terapi.

INTRODUCTION

Atopic dermatitis (AD) is defined as a chronic inflammatory skin disease characterized by recurrent eczema followed by intense itch resulting in decreased quality of life. Global Disease Burden project ranks AD as the skin disease with the highest rating of the total global disability burden.[1] Studies show a total female to male ratio of 1:3.[2] Adolescents and adults have a lower prevalence than children.[3] The level of AD severity and morbidity may vary based on age, gender, socioeconomic status, geographical region, and ethnicity. The prevalence of AD in urban areas and high-income countries is significantly higher compared to rural areas and low-income countries.[4]

A comprehensive understanding of its pathogenesis is essential as the nature of this disease is multifactorial and complex. Pathogenesis of AD consists of varying genetic components that affect skin conditions and could be exacerbated by defects in the epidermal barrier due to environment and lifestyle. Further, the alteration of immune response and the microbial balance of the skin occurred and produced moderate to severe AD disease. These different changes on the genetic level, including the alteration of the immune system become the foundation of the approach to treat AD according to its different phenotypes and endotypes.[5,6]

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Current research is concentrated on targeting different cytokines involved in major immune axis in AD's clinical manifestation, through monoclonal antibody as a novel systemic therapeutic drug. Monoclonal antibody could directly bind toward specific interleukin or modulate the cell response which further changes the immune response dynamic.[7] This study aims to summarize the recent update on the pathogenesis of AD and management of moderate-to-severe AD; and focus on the development of monoclonal antibodies as a novel systemic therapeutic drug.

METHOD

In this article, we conducted a systematic search of several database to identify relevant studies published from 2013 to 2023. Several of these database includes EMBASE, EBSCOhost, PubMed, Scopus, and Wiley Online Library. Further, 1196 studies were included in our analysis, and quality was assessed using the Newcastle-Ottawa Scale. A total of 38 studies were included in our systematic review. Keywords used include "monoclonal antibody" AND "therapy" AND "atopic dermatitis". Manuscripts are classified as relevant if discuss various updates in aspects of AD management and the use of monoclonal antibodies. The review procedure is summarized in **Figure 1.**

RESULTS AND DISCUSSION

Pathogenesis of Atopic Dermatitis

Many research studies have attempted to explain the pathogenesis of this disease. There is a relationship between deficiency of skin protection (barrier), changes in the immune system, and pruritus, each of which contributes to the development, progression, and chronicity of this disease **(Figure 2).**[5,6]

The attachment of various molecules to the process of disrupting skin protection, such as innate lymphoid cells 2 (ILC2), basophils, eosinophils, and also mast cells explains the pathogenesis of atopic dermatitis related to the immunological aspect.[7] Disruption of skin protection and entry of allergens cause the production and release of cytokines originating from the epithelium, including thymic stromal lymphopoietin (TSLP), interleukin-25 (IL-25), and interleukin-33 (IL-33). After ligation of the above molecules with receptors on ILC2, namely the TSLP receptor (TSLPR), IL-25 receptor (IL-25r also known as IL7RB), and IL-33 receptor (IL-33R or ST2), ILC2 will be activated to release T-Helper 2 (Th2) cytokines such as IL-5 and IL-13.[8] In addition, IL-4 released by basophils, which is found adjacent to ILC2 at the site of atopic dermatitis lesions, is able to activate ILC2 directly. PGD2, hypothesized to originate from mast cell degranulation, also contributes to the recruitment of ILC2 to the skin as well as the induction of ILC2 cells to produce Th2 cytokines through attachment to the CRTH2 receptor.[9] In contrast, cell adhesion molecules namely E-cadherin, in keratinocytes have an inhibitory effect on ILC2. Even so, the loss of the E-cadherin molecule is found in individuals with filaggrin deficiency (FLG) so skin inflammation continuously increases due to an imbalance of excessive increases in excitatory stimulus and reduced inhibitory stimulus.[10]

Any abnormalities related with filaggrin structure can further increase inflammation in the skin through various mechanisms as summarized in **Figure 2** On the other hand, changes in Th2 phenotype expression are caused by disruption of the skin barrier and keratinocyte lesions that trigger TSLP, Th2, a chemical signal recruiting eosinophils together with IL-33 and IL-25, to be released from keratinocytes. Furthermore, the loss of the acid mantle on the epidermis also triggers TSLP secretion through activation of protease-activated receptor type 2 (PAR-2) through increased serine protease. Increased allergen penetration and microbial colonization activate various inflammatory molecules and Th17 pathways, which culminate in complicating the pathogenesis of AD in advanced stages. In addition, abnormalities in the molecular constituents of the stratum corneum, as well as abnormalities in the structure of the zonula occludens, can precipitate and/or promote inflammation on the skin. As elaborated in **Figure** 2, the

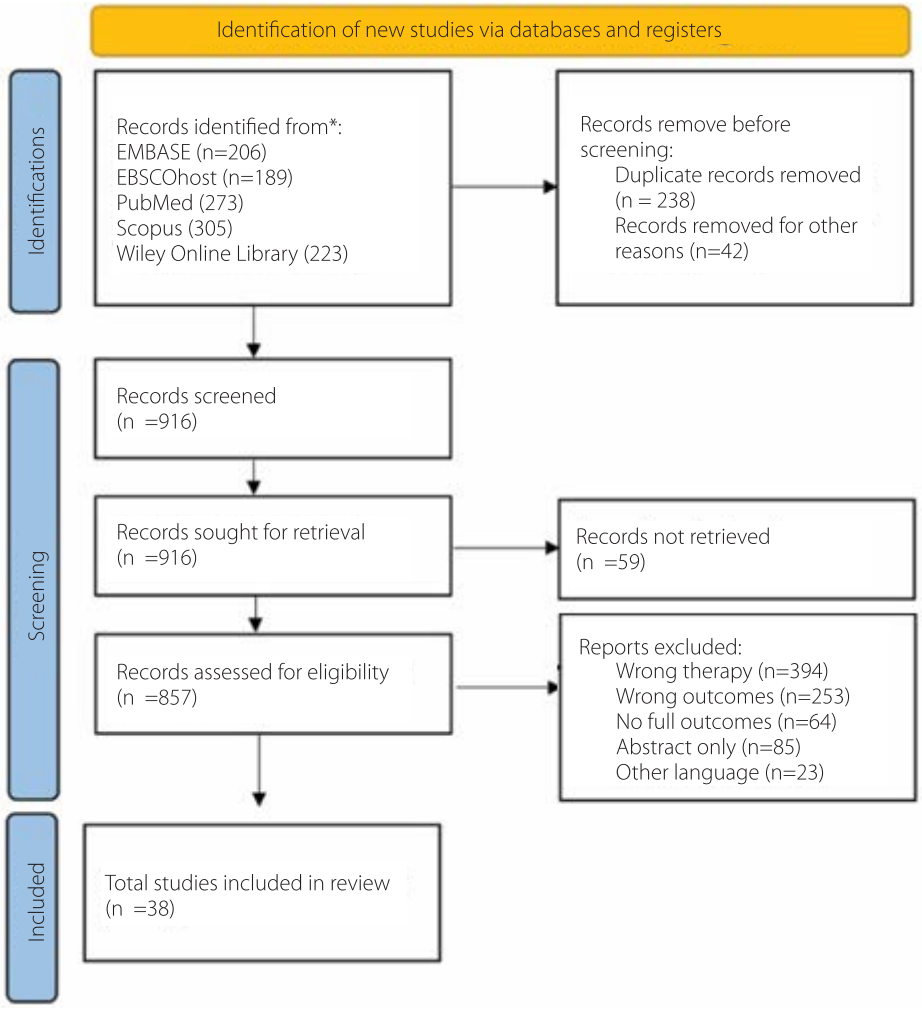

Figure 1. PRISMA flow diagram.


inflammation causes continued damage to the skin barrier dysfunction through regulation that reduces the release of essential molecules in maintaining this barrier. Pruritus in AD can also be caused by hyperinnervation of the epidermis, increased pruritogen, and central sensitization which can cause damage to skin integrity and promote inflammation. However, until now there is still no medication or management that completely cures AD. Many clinical trials of biological agents have been carried out and are expected to be a therapeutic option of AD in the future.[10]

Current Approach and Issues in the Management of Patients with Atopic Dermatitis

The management of atopic dermatitis begins with non-pharmacological treatments to moisturize the skin and to improve the structure and function of the skin as a barrier. In conjunction, behaviour modification and patient education are equally important to achieve optimal results. **Figure 3** illustrates the AD management algorithm. For AD cases with mild severity, topical corticosteroids are the gold standard in terms of their efficacy and safety profile. Topical therapy remains the first choice for treating AD.[11] The most common agents are topical corticosteroids which suppress proinflammatory cytokines by acting on immune cells such as dendritic cells, monocytes, and macrophages. A variety of different corticosteroids that can be used, each with its own potency, efficacy, and safety profile.[12] The choice depends on several factors such as anatomic area, therapeutic response, and potential side effects. Topical steroids should be combined with emollient applications. However, topical steroids are not suitable for long-term use because of various side effects such as atrophy, striae, corticosteroid-induced glaucoma, and perioral dermatitis.[13]

Another topical therapy is a topical calcineurin inhibitor (TCI) which also acts as an anti-inflammatory by inhibiting calcineurin-dependent activation of T lymphocytes. Two often used TCIs are tacrolimus ointment and pimecrolimus cream.[14] TCI can be used to treat acute and chronic atopic dermatitis of varying severity; can be used as a stand-alone agent or in conjunction with topical corticosteroids. However, the safety of prolonged use of TCI has not been established.[15] In addition, AD patients are more susceptible to skin infections, especially *Staphylococcus aureus*, which may necessitate topical antibiotics. However, topical antibiotics use is still controversial with contradictory conclusions.[16]

Relatively new topical agents are PDE4 inhibitors which act by suppressing cytokines and reactive oxygen species (ROS) production. However, PDE4 inhibitors are only approved for mild to moderate cases.[17] In addition to topical treatments, oral therapy is also available. Higher severity cases with large surface area involvement or resistance to conventional treatment were subjected to a systemic approach. The first is oral antibiotics after the diagnosis of infection has been evaluated and established. Histamine secreted by mast cells results in vasodilation and pruritus. This itching causes scratching which further exacerbates the pruritus due to the 'itch-scratch cycle'. Antihistamines may be administered to provide sedation, however, there is no evidence of the antihistamines' effect on the underlying pathogenesis.[18]

Most AD patients respond well to general treatment regimens that include environmental modifications, non-pharmacological approaches, and conventional topical therapies; a maintenance therapy can be given as a follow-up if a relapse occurs.[19] Some patients, especially those with frequent relapses, require a different approach such as systemic immunomodulators, such as cyclosporine A (CSA). CSA is effective as a short-acting agent with a rapid onset of action but is not recommended as maintenance therapy due to its side effects. The major drawback of these systemic drugs is their broad immunosuppressive activity and thus, their increased risk profile.[20] With advances in understanding the complex processes of immune signalling in atopic dermatitis, many potential targets are now being identified **(Figure 4).** Three main immune pathways, Th2, Th22, and Th17/IL-23, are the potential target for atopic dermatitis drug development **(Table).**[16]

Drug Development Targeting the Th2 Immune Pathway.

First, in the Th2 immune pathway, the main targets are IL-4 and IL-13, IL-31, TSLP, OX40, and IL-33. Starting with IL-4, dupilumab is a capable IL-4 receptor antagonist that inhibits IL-4 and IL-13 cytokine signaling and has been approved in European and American countries for adults with moderate to severe cases of AD.[21] Currently, phase III clinical trials are conducted in pediatric patients (NCT02612454) from 6 months to 18 years of age.[22] Another promising clinical trial developed around IL-4 was study of AK120 (IL-4Rα) with completed phase 1 and already started phase 2 with the name of manfidokimab in 2021.[23]

Another drug, tralokinumab, also inhibit IL-13 but through IL-13 receptor (IL-13R) blockade, with its efficacy and safety confirmed in

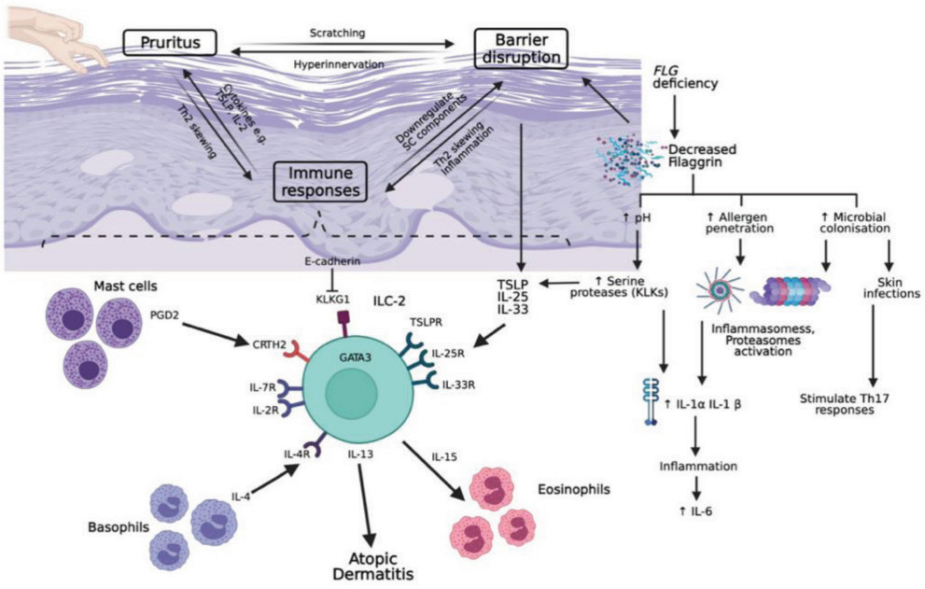

Figure 2. Pathogenesis of atopic dermatitis.[5-10]

adults and currently proven had similar effects through phase 3 in adolescent .[24] In 2022, five clinical trials utilizing tralokinumab for AD show that the drug was well tolerated for moderate-to-severe AD and consistently safe during treatment.[25] Meanwhile, the specific IL-13-Rα1 blocker known as eblasakimab passed phase 1a with promising result and initiate phase 2B (NCT05158023) in 2022.[26]

The IL-31 receptor monoclonal antibody, nemolizumab, showed promising potential

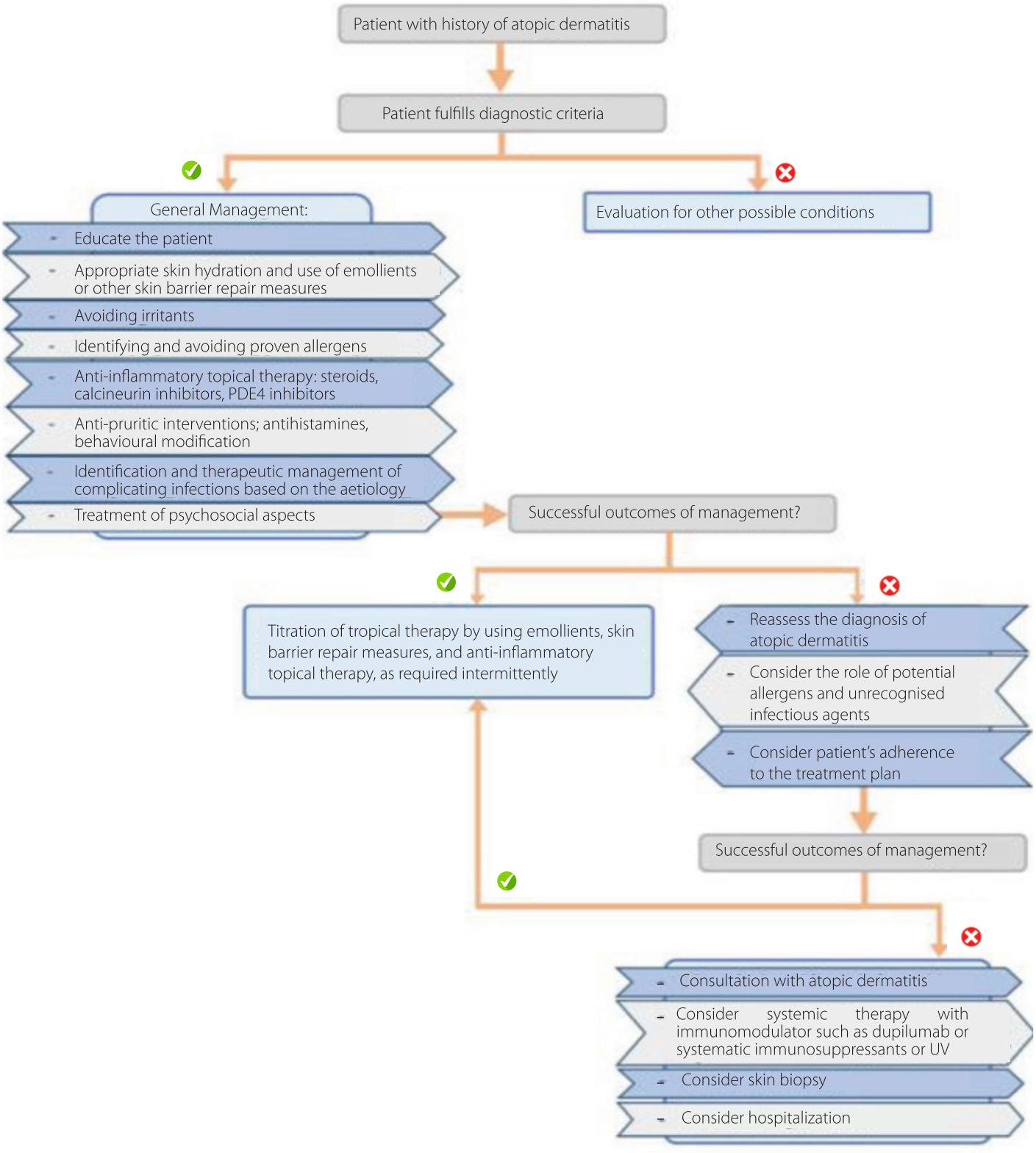

Figure 3. The AD management algorithm is adopted from Simpson EL, *et al.*[24]


in clinical trials by a significant reduction in pruritus scores based on phase II clinical trials (NCT03100344).[27] In 2020 a phase III trial with subcutaneous nemolizumab combined with topical agents shown to have a higher reduction in pruritus compared to placebo.[28] Another compound named BMS-981164 effects found to be depend on the DPP-4 level in the blood.[29] Patients with high levels of DPP-4 experienced a significant increase in clinical scores while the increase was not significant in sub-populations with low DPP-4 blood levels.[30] In addition to dupilumab and tralokinumab, an IL-13 inhibitor with the name lebrikizumab, managed to achieve a promising clinical response based on the phase II clinical trial (NCT03443024).[31] Meta-analysis of the efficacy and safety of lebrikizumab as monotherapy in 2023, showed that it improved EASI scores significantly and did not contribute to any incidence of AEs or mortality.[32]

Another target is known as thymic stromal lymphoprotein (TSLP), but only two drugs currently are under development, tezepelumab and MK-8226 (targeting the TSLP receptor). In phase II clinical trials, tezepelumab failed to reach the primary clinical trial endpoint and was shown not to significantly increase the EASI (Eczema Area and Severity Index) score (NCT02525094).[33] Meanwhile, the full potential of MK-8226 has not been discovered because the phase I was stopped due to company financial reasons (NCT0173251).[34]

OX40, which belongs to the TNF receptor family, is a cell surface glycoprotein expressed by CD4 T cells and subsequently generates costimulatory signals for T cell activation. Two drugs under development are GBR 830 and KHK4083.[35] GBR 830 is known to have beneficial long-term effects for the treatment of severe AD (NCT02683928).[36] Another drug in this class, KHK4083, already completed the phase I clinical trial stage (NCT03096223) and recently released its result of phase 2b study (NCT03703102) under the name of rocatinlimab which shows improvement of AD condition even after treatment discontinuation and was well tolerated.[37] Another developing drug was amlitelimab (KY1005, SAR445229) which belongs to nondepleting anti-OX40Ligand (OX40L), shown to reduce IL-13 serum levels during phase 2a clinical trial (NCT03754309) in 2020 and planned to start phase 2b.[38] The final target on the Th2 pathway is IL-33, where ANB020 showed significant clinical efficacy based on phase II clinical trials.[39]

Drug Development targeting the Th22 Immune Pathway

In the Th22 pathway, the only drug developed is fezakinumab, an IL-22 monoclonal antibody that has been proven effective for severe AD based on phase 2 clinical trials (NCT01941537) and well tolerated.[40]

Drug Development targeting the Th17/IL-23 Immune Pathway.

The trial on Th17/IL-23 pathway consists of three drugs each with a different target. The first is ustekinumab which targets IL-12/23p40, secukinumab which targets IL-17A and MOR1106 which targets IL17C.[41] Ustekinumab showed no significant improvement, while MOR1106 offered a more promising response rate and secukinumab is still undergoing phase II clinical trials (NCT02594098).[42]

Alternative Strategies

Other types of drugs known as agents with broader inhibitory properties have come into the spotlight due to the understanding that AD is characterized by the activation of several different immune pathways.[43]Janus Kinase (JAK) Inhibitors was also used, oral baricitinib, upadacitinib, and abrocitinib have shown to have similar safety and efficacy with monoclonal antibody in improving moderate-to-severe AD condition.[44] The

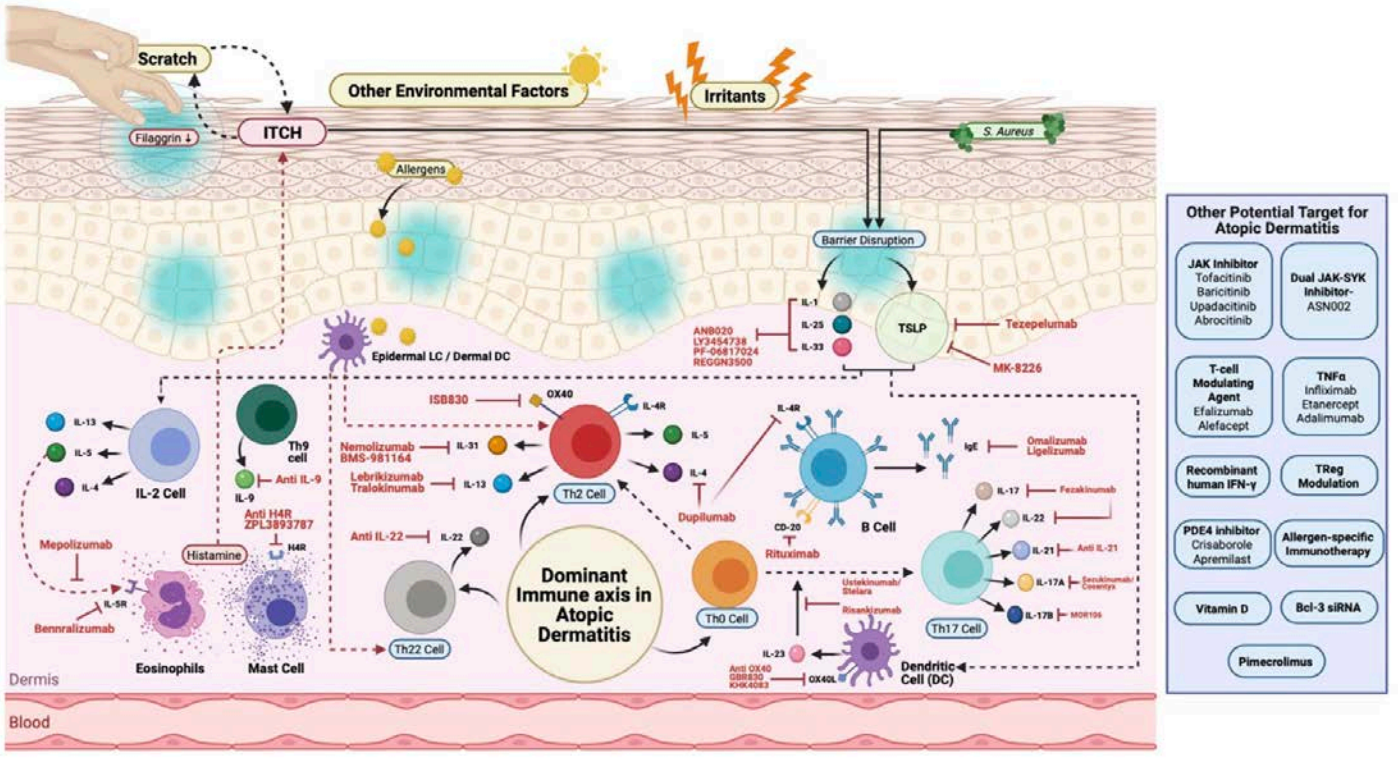

Figure 4. Various target cells and pathways available for individualized therapeutics in AD. [16,21-48]

Table. Study characteristic and outcomes.

NO.	AXIS	MAIN TARGETS	MONOCLONAL ANTIBODY	AUTHOR, YEAR	STUDY TYPES	POPULATION	CLINICAL TRIAL NUMBER	RESULT
1	Th2	IL-4R	Dupilumab	Cork MJ, *et al*. 2020.	Randomized clinical trial (RCT)	880 adolescents	NCT02612454	Phase III open-label extension in adolesecents confirmed that Dupilumab has similar efficacy and safety profile as in adults
2	Th2	IL-4Rα	Manfidokimab (AK120)	Wang G, *et al*. 2021.	Randomized clinical trial (RCT)	180 adults	NCT06092762	Ongoing phase 2 clinical trial
3	Th2	IL-13R	Tralokinumab	Paller AS, *et al*. 2023.	Randomized clinical trial (RCT)	289 adolescents	NCT03526861	Phase III trials confirmed clinical benefit and safety of Tralokinumab to be similar as in adults.
4	Th2	IL-13R	Lebrikizumab	Guttman-Yassky E, *et al*. 2020.	Randomized clinical trial (RCT)	280 adults	NCT03443024	Phase 2b trials shows rapid, dose-dependent efficacy and demonstrated a favorable safety profile.
5	Th2	IL-13-Rα1	Eblasakimab	Cevikbas F, *et al*. 2023.	Randomized clinical trial (RCT)	302 adults	NCT05158023	Phase 1a clinical trial shows promising efficacy to block IL-13-Rα1 with no significant adverse effects
6	Th2	IL-31	Nemolizumab	Silverberg JI, *et al*. 2020.	Randomized clinical trial (RCT)	226 adults	NCT03100344	Phase 2 clinical trial shows rapid and sustained improvements within patients with acceptable safety profile.
7	Th2	DPP4	BMS-981164	Patel, *et al*. 2021.	Randomized clinical trial (RCT)	93 adults	NCT01614756	No conclusive results from phase 1 trial
8	Th2	TSLP	Tezepelumab (AMG 157/ MEDI9929)	Simpson, *et al*. 2019.	Randomized clinical trial (RCT)	113 adults	NCT02525094	Phase 2 failed to show promising result
9	Th2	TSLP	MK-8226	Renert-Yuval, *et al*. 2019.	Randomized clinical trial (RCT)	65 adults	NCT0173251	Phase 1 stopped due to company financial issues
10	Th2	OX40	GBR 830	Guttman-Yassky *et al*, 2019	Randomized clinical trial (RCT)	64 adults	NCT02683928	Two doses of GBR 830 administered 4 weeks apart were well tolerated and induced significant progressive tissue and clinical changes until day 71
11	Th2	OX40	Rocatinlimab (KHK4083)	Guttman-Yassky, et al. 2023.	Randomized clinical trial (RCT)	274 adults	NCT03703102	Phase 2b shows improvement of AD condition even after treatment discontinuation and was well tolerated
12	Th2	OX40	Amlitelimab (KY1005, SAR445229)	Weidinger, *et al*. 2023.	Randomized clinical trial (RCT)	89 adults	NCT03754309	Amlitelimab was well tolerated and resulted in clinically meaningful improvements in AD , ongoing phase 2b clinical tria
13	Th2	IL-33	ANB020	Londei, *et al*. 2017.	Randomized clinical trial (RCT)	96 adults	NCT02920021	Significant clinical efficacy based on phase I clinical trials and enrolling on phase 2a
14	Th22	IL-22	Fezakinumab	Guttman-Yassky E, *et al*. 2018.	Randomized clinical trial (RCT)	22 adults	NCT01941537	Effective for severe AD based on phase 2 clinical trials and well tolerated
15	Th17/ IL-23	IL-12/23p40	Ustekinumab	Saeki H, *et al*. 2020.	Randomized clinical trial (RCT)	79 adults	NCT01945086	Phase II clinical trial shows nonsignificant improvement change from baseline EASI score.


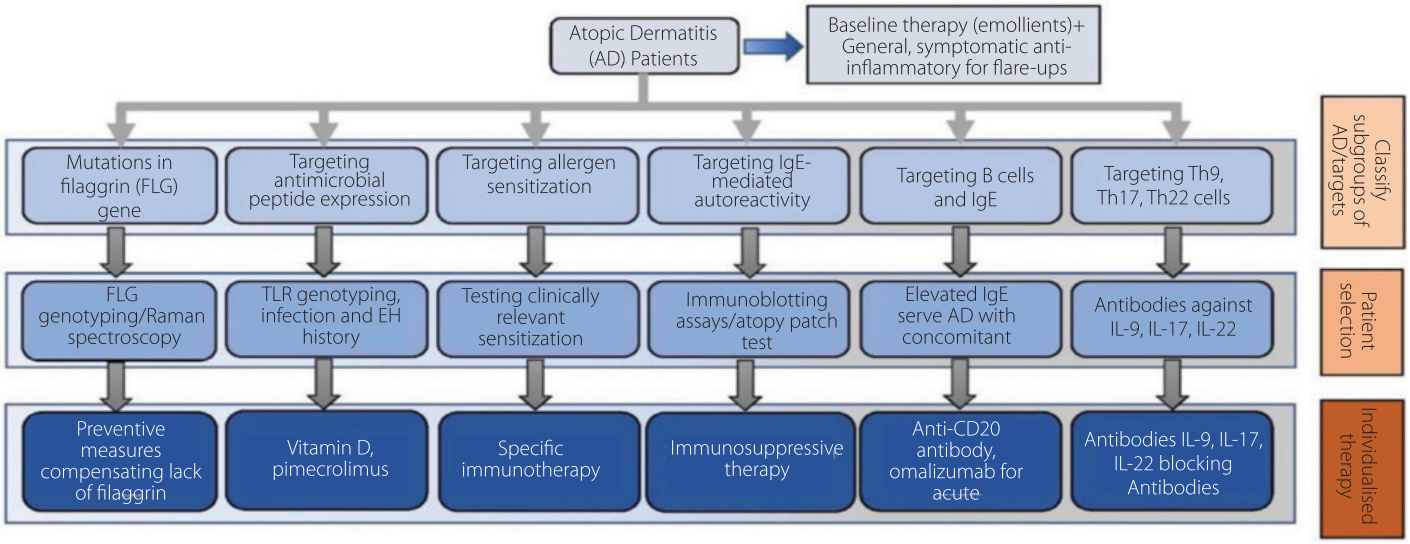

Figure 5. Schematic diagram of a potential subgroup of patients with AD. [7,8,43,49]

newer topical JAK inhibitor such as ruxolitinib (JAK1/2) and delgocitinib (pan-JAK) are currently being approved in several countries for AD management.[45] However, the long-term durability and safety are still become topic of debate with additional challenges for implementation as its need molecular phenotyping to determine the most suitable subgroups.[46]

Another class of drugs in atopic dermatitis cases that are currently being developed are Histamine 4 Receptor Antihistamines; antagonists at histamine receptor subtype 4 (H4R), known to play a role in pruritus and inflammation caused by Th2 and Th17. The only compound under investigation in this class of drugs is an oral H4R antihistamine, ZPL-3893787 which showed promising clinical efficacy in phase II clinical trials while clinical trials for safety and efficacy alone (NCT03948334) are still in progress.[47] Exciting development arise by the possibility of combined therapy shown by the randomized phase 3 clinical trial; combination of lebrikizumab and topical corticosteroids proved to be safe and significantly improved outcomes compared with topical corticosteroids alone.[48] A schematic diagram depicting the AD patient subgroups together with the main pathogenic factors and individual therapy is shown in Figure 5.[49]

Conclusion

The current landscape of AD is changing tremendously as the pathogenesis of AD is continuously uncovered. The renascence of atopic dermatitis therapeutics with one of the most promising was the utilization of monoclonal antibodies specifically antagonistic to certain cytokines.

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