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Atopic Dermatitis: Disease Burden, Pathophysiology, and Use of Dupilumab for Treatment

Dr. Ignasi Figueras of Bellvitge Hospital, University of Barcelona, and Dr. Chih-ho Hong of St. Paul's Hospital, Vancouver, provide the considerations of using dupilumab for therapy and a closer look at the atopic dermatitis disease burden, respectively

Atopic dermatitis (AD) is a common chronic inflammatory skin disease that has a significant impact on patients and their families[1]

AD is characterised by pruritus and skin lesions that typically affect the face, neck, arms, and legs[1]

AD impacts daily activities and work productivity, accounting for a substantial portion of the global burden generated by skin disease[1,2]

Almost 25% of patients with AD suffer from anxiety[3]

About 38% of patients with moderate-to-severe AD feel that their disease has prevented them from choosing a specific career[4]

The disease has a significant effect on a patient's mental health

1 in 4 patients with AD exhibit symptoms of depression[3]

1 in 8 patients with AD experience suicidal ideation[3]

Severity of AD symptoms

Impact on quality of life[5]

Patients with AD also suffer from skin infections[6]

Skin barrier defects[6]

Colonisation by *Staphylococcus aureus*[6]

- *S. aureus* produces toxins
- These break down the skin barrier and facilitate immune dysregulation

Causes of skin infection

Cutaneous dysbiosis[6]

- Deficiency of commensal bacteria
- Virulence by *S. aureus*

Immune dysregulation[6]

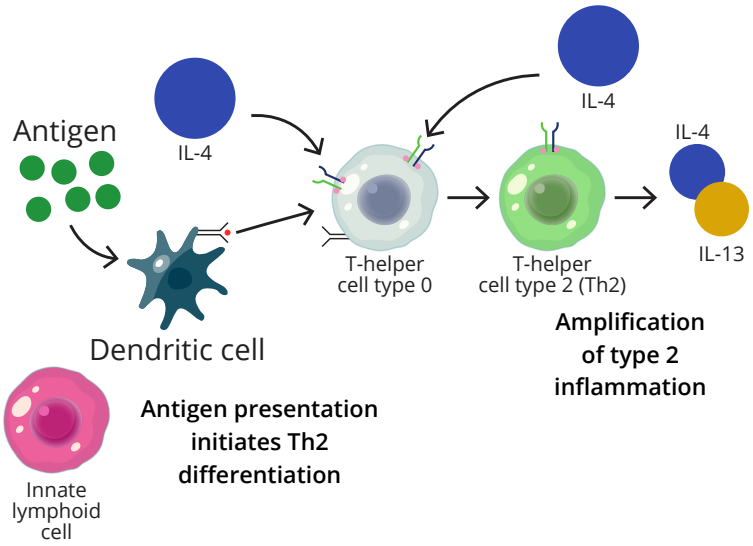
- Skewed immune responses
- Impact cutaneous immunity

Increased financial burden on patients[7]

Skin infections in AD

Greater utilisation of and burden on healthcare services[7]

Pathophysiology of AD: Role of IL-4 and IL-13



Interleukin-4 (IL-4) plays an important role in:

- Activation of B-cells and the type 2 inflammatory response[8,9]
- Expression of IL-13[8,9]

IL-4 and IL-13 play an important role in[10,11,17,19]:

- Barrier dysfunction and tissue remodelling[10,17,18]
- Neuroimmune dysfunction[17-19]
- Smooth muscle contractility[11]
- Microbiome alterations[17]
- Mucous production[11,17]
- Immunoglobulin E (IgE) production[2]
- Transport of inflammatory cells to tissues[11,17,18]

How does AD occur?[9,20-25]

External allergens and antigens penetrate the epidermis

↓

Absorbed by Langerhans dendritic cells

↓

Migrate to lymph nodes

↓

Production of alarmins

↓

Switch to type 2 inflammatory response

↓

Lymphocytes migrate back to the dermis

↓

IL-4 / IL-13

Initiate production of IL-4 and IL-13

↓

Worsening of barrier disruption

↓

Pruritus and itching[20,21]

IL-4

Changes in the skin microbiome

↓

Drive type 2 inflammation and skin barrier disruption[20,21]

↓

Colonisation by *S. aureus* causes:

- Type 2 inflammation
- Host cytotoxicity
- Mast cell activation
- IgE production
- Keratinocyte alarmin (thymic stromal lymphopoietin, IL-25, and IL-33) production
- Epidermal barrier disruption[20,24,25]

Blocking action of IL-4 and IL-13 can stop itching[20,21,26]

Figure adapted from Li W, *et al*. (2020)

Long-term AD therapy and its real-world impact

The long-term use of conventional systemic therapies for moderate-to-severe AD poses some roadblocks[27-29]

- Length of treatment with systemic immunosuppressants is limited by adverse side effects and possibility of disease reoccurrence post treatment withdrawal
- Patients may experience intensified disease activity for 30%–50% of the year

Historically, AD treatments (oral corticosteroids/immunosuppressants) have been used via a reactive, episodic approach[27-29]

Therefore, there continues to be a need for AD therapies that overcome these roadblocks

Dupilumab in AD[9]

Dupilumab:

Is a fully human monoclonal antibody

↓

Targets the IL-4Rα subunit

↓

Blocks IL-4 and IL-13 receptors

↓

Inhibits IL-4 and IL-13 signalling and prevents cytokine function

↓

Relieves disease symptoms[9]

Long-term disease control with dupilumab is supported by real-world evidence using studies conducted across 30 countries

The ADRN09 study[26]

6 weeks

Multi-centre randomised double blind study evaluating the impact of dupilumab administration

→

Dupilumab treatment[26]:

- Reduced *S. aureus* counts in as little as 3 days with significantly better results after 14 days
- Improved infection symptoms
- Reduced *S. aureus*-related cytotoxin activity
- Improved skin barrier function

The BALISTAD study[30]

16 weeks

Exploratory study evaluating the effect of dupilumab on barrier function and lipid characteristics of the skin barrier

→

Dupilumab treatment[30]:

- Restored skin barrier function
- Was associated with an improvement in signs, symptoms, and quality of life in patients with AD

The CHRONOS study[31]

52 weeks — Study evaluating the safety of dupilumab compared to placebo → 204 weeks — Open-label analysis[31] of the CHRONOS study evaluated safety → 52 weeks ✓ 204 weeks ✓ — Long-term use of dupilumab was reported to be safe at both time points

Adverse events (AEs) reported at 1 year were similar to those reported at 4 years

Common AEs reported:

- Nasopharyngitis
- Upper respiratory tract infection
- Conjunctivitis

Results at year 4 also indicated reduced rates of total herpesvirus infections, eczema herpeticum, and herpes zoster[31]

Dupilumab is approved for the treatment of adults with moderate-to-severe AD[27-29] in 60 countries

Dupilumab can significantly reduce the prevalence of skin infections (bacterial, fungal, and viral) after 12 months of use (from 24.7% to 11.2%)[32]

Open dialogue, easy explanation of benefits and safety, patient testimonies, and making patients comfortable with disease discussion are essential in increasing patient consideration for long-term use of dupilumab

Concluding remarks

- The cumulative disease burden of AD can have a substantial impact on the career choices, mental health, and quality of life in patients with AD; this increases with disease severity
- The pathophysiology of AD is driven by systemic type-2 inflammation, with cytokines IL-4 and IL-13 mediating the disease's effect on immune response, skin barrier dysfunction, and itching
- Treatment with dupilumab resulted in improvements in skin barrier function, disease activity, cytotoxin reduction, and quality of life outcomes in patients with AD
- The long-term efficacy of dupilumab is supported by real-world studies worldwide

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