IgE Modulation and Disease Severity in Atopic Dermatitis Treated with Methotrexate

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The authors declare no conflict of interest.

Learning Objectives

- ***Does methotrexate treatment for atopic dermatitis still hold intrinsic value in its treatment?***
- ***While biologics are theoretically capable of modifying disease progression, do other treatments for atopic dermatitis offer similar potential in terms of biomarkers?***

Background

✓ Atopic dermatitis (AD)

- Chronic relapsing inflammatory skin disease
- Characterized by intense pruritus and association with allergic diseases

✓ Methotrexate (MTX)

- Originally developed as an **antimetabolite anticancer drug**
- Based on its **immunomodulatory effects**, it is also used to treat various autoimmune diseases such as atopic dermatitis, rheumatoid arthritis, psoriasis, and Crohn's disease
- **Inhibit dihydrofolate reductase (DHFR),** thereby **blocking DNA synthesis** and **suppressing T-cell proliferation**
- **Induce anti-inflammatory adenosine release**, leading to **suppression of inflammatory responses**

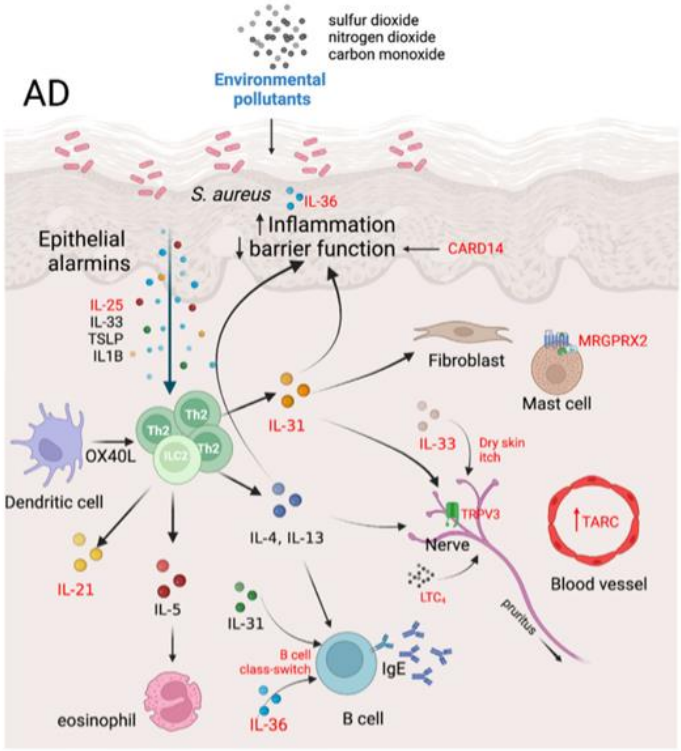

FIG 1. Novel insights and additions to AD pathogenesis *(red)*, environmental contribution *(blue)*, and their relevance to key AD-associated features, including T_H2 immune responses, epidermal inflammation and barrier function, mast cell activation, and pruritus. *LTC_4*, Leukotriene C_4; *MRGPRX2*, Mas-related G protein–coupled receptor X2; *TARC*, thymus and activation-regulated chemokine; *TSLP*, thymic stromal lymphopoietin.

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Objectives

✓ **Methotrexate (MTX) Treatment in Atopic Dermatitis (AD)**

- Systemic therapeutic option for moderate-to-severe or treatment-refractory AD patients who exhibit insufficient response to conventional therapies such as topical corticosteroids, calcineurin inhibitors, or phototherapy.
- Recent studies have demonstrated that MTX reduces key inflammatory cytokines, including **IL-31, TARC,** and **CTACK**, leading to clinical improvement of eczematous lesions.
- However, there is a lack of systematic evaluation regarding serum biomarker changes following MTX therapy in AD patients.

➤ This study aims to assess changes in serum biomarkers — **IgE, D1, D2**, and **M227**— after systemic MTX treatment in patients with AD, and to determine their clinical significance.

Methods and Materials

Retrospective single-center observational study

AD patients

+

- **methotrexate (MTX)**

+

Serum secific IgE
(ImmunoCAP®)
Serum eosinophils

- Total IgE
- Eosinophil count
- House dust mite specific IgE
- Malassezia specific IgE

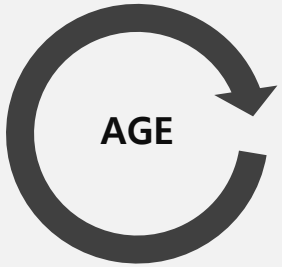
Analysis of patients' **medical records** and **blood test results**

Evaluation of **changes** in **serum biomarkers before and after treatment (6 months)**

Results

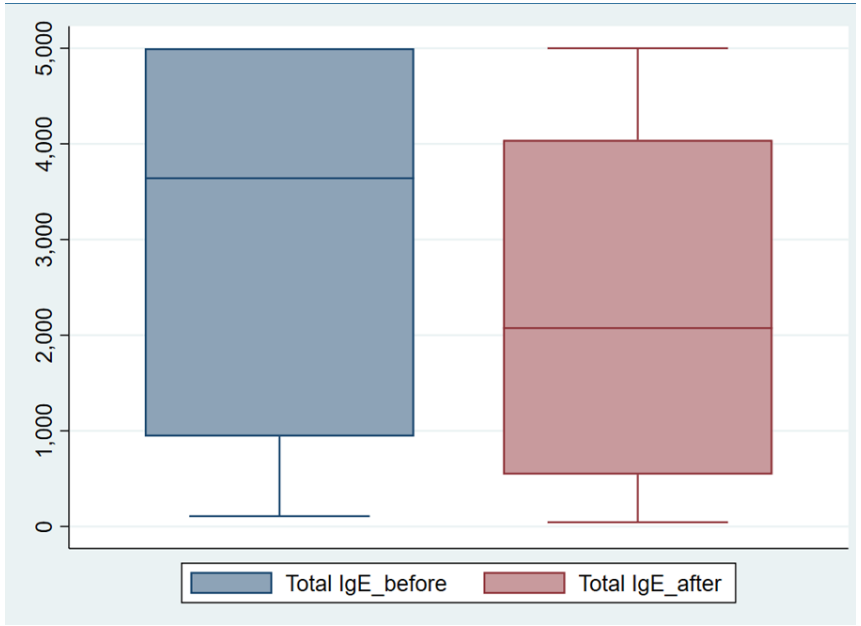
✓ **Baseline Characteristics**

MTX: Male 21, Female 7



MTX: 30.9 (16-78)

Total IgE after 6 months



paired t-test

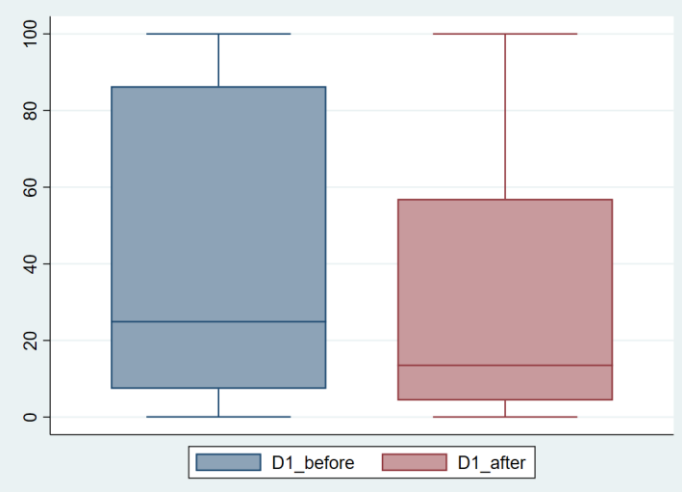
3107.0 ± 1980.893 IU/mL

↓

2449.97 ± 1908.21 IU/mL *(p=0.0107)*

Results: Before & After 6 months

Dermatophagoides pteronyssinus



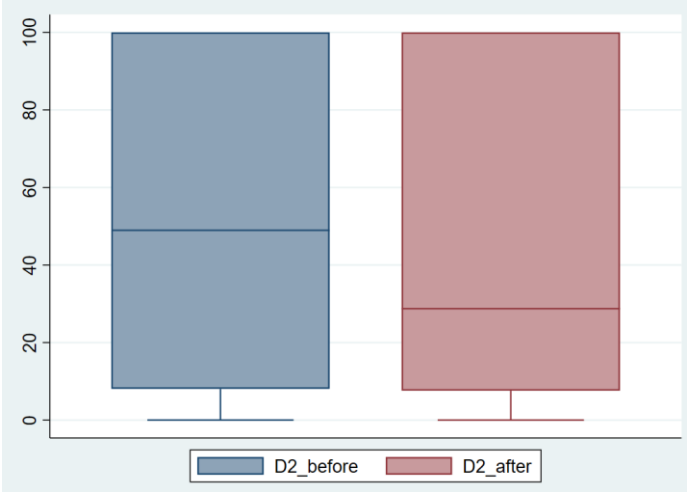
paired t-test

38.92 ± 38.72 kUA/L

↓

31.42 ± 34.97 kUA/L *(p=0.0075)*

Dermatophagoides farinae



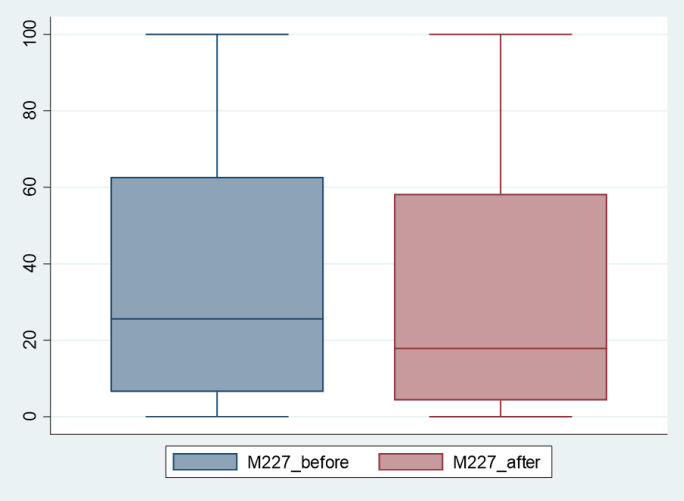
paired t-test

50.31 ± 43.52 kUA/L

↓

46.59 ± 43.26 kUA/L *(p=0.3235)*

Malassezia spp.



paired t-test

36.08 ± 32.58 pg/mL

↓

31.82 ± 32.82 pg/mL (*p=0.2072*)

Discussion

✓ Total IgE

- A representative marker of Th2 immune response in AD, as B cells produce IgE under the stimulation of IL-4 and IL-13
- In this study, a significant reduction in Total IgE after MTX treatment suggests that MTX suppresses Th2 cytokine pathways by inhibiting folate metabolism, modulating T- and B-cell functions, and enhancing adenosine production, thereby exerting anti-inflammatory effects

✓ Specific Dermatophagoides pteronyssinus IgE (D1) levels also decreased significantly

- This indicates a reduction in IgE reactivity to specific allergens
- D1 and D2 tests, based on skin or serum allergen-specific IgE measurements, are used to assess allergic sensitization
- The decrease in D1 levels observed in this study suggests that MTX may influence allergen-specific immune responses in addition to its anti-inflammatory action
- These findings imply that MTX could contribute not only to inflammation control but also to attenuation of allergen-driven responses

Discussion

✓Immune Response and Inflammatory Markers of Atopic Dermatitis

- **IgE**: Immunoglobulin associated with allergic responses, observed at elevated levels in AD patients.
  - The most extensively studied biomarker in AD, although its correlation with disease severity is weak
  - In some moderate-to-severe cases, IgE levels are elevated, while in intrinsic AD, IgE may remain within normal range, limiting its use as a disease-monitoring marker
  - Allergen-specific IgE/total IgE ratio has been suggested as a potentially more reliable biomarker for certain allergens
- **Soluble IL-2 Receptor (sIL-2R):**
  - Serves as a marker of T-cell activation, associated with inflammatory responses in AD
- **C-Reactive Protein (CRP):**
  - A general inflammatory marker, useful for assessing the overall systemic inflammation in AD.
- **Eosinophil Cationic Protein (ECP):**
  - A marker of eosinophil activation, reflecting inflammatory activity in AD

Dermatol Ther (Heidelb). 2024 Jul;14(7):1729-1738
Journal of Clinical Medicine. 2022; 11(16):4639

Limitation

✓ Data were retrospectively collected from a single institution

- Potential selection bias and limitations in data collection

✓ Certain biomarkers had measurement limits (e.g.,'>5000' or '>100'), leading to exclusion or correction in the analysis, which may have affected data accuracy

✓ This study focused on quantitative changes in biomarkers;

- However, direct comparison with clinical severity indices (EASI, SCORAD, etc.) was not performed,
- Limiting the interpretation of how biomarker reduction correlates with actual clinical improvement.

Conclusion

- ✓ This study **quantitatively demonstrated** the **changes in serum biomarkers** reflecting the **immunological effects of methotrexate** in **real-world clinical settings**.
- ✓ These findings may serve as valuable preliminary data for future large-scale prospective studies and for the development of **biomarker-based personalized treatment strategies**.
- ✓ Current AD treatments do not adequately account for the **diverse phenotypes and endotypes**, underscoring the need for personalized therapeutic approaches.
- ✓ To address this, **biomarkers are expected to play a key role** in **classifying AD patients** and in establishing **personalized treatment strategies.**
- ✓ In complex diseases like AD, **combinational biomarkers**, rather than single markers, may provide more **reliable diagnostic and therapeutic insights.**

Q & A