Eosinophilic complications during dupilumab therapy for type 2 diseases: a systematic review

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Background - Type 2 Inflammation

- Type 2 inflammation targets parasites, venoms and toxins.
- Type 2 chronic inflammatory diseases:
  - Asthma
  - Chronic rhinosinusitis with nasal polyps (CRSwNP)
  - Allergic rhinitis
  - Atopic dermatitis (AD)
  - Eosinophilic esophagitis (EoE)

Appendix: Types of Inflammation

INFLAMMATORY PATHWAY	TYPE 1	TYPE 2	TYPE 3
Primary immune cells	Macrophage, Th1, ILC1, NK	Th2, ILC2, Mast cell, Basophil, Eosinophil	Neutrophil, Th17, ILC3
Key cytokines	IFNγ, TNF, IL-6, IL-12, IL-18, IL-2	IL-4, IL-5, IL-13, IL-31	IL-17, IL-6, IL-22, IL-23
Function	• Antitumor activity • Cellular immunity: antiviral/antibacterial • Suppression of type 2	• Humoral immunity: antiparasitic helminths • Neutralizes toxins • Regulates wound repair and regeneration • Suppression of type 1	• Regulation of intestinal epithelial barrier • Responses to extracellular bacteria and fungi
Examples of consequence of dysregulation and associated disease	• Ankylosing spondylitis • Atherosclerosis • Autoimmune gastritis • Diabetes mellitus • Hashimoto thyroiditis • Inflammatory bowel disease • Multiple sclerosis • Rheumatoid arthritis • Sarcoidosis	• Allergy • Anaphylaxis • Type 2 asthma • Atopic dermatitis • Chronic obstructive pulmonary disease with type 2 inflammation • Chronic rhinosinusitis with nasal polyps	• Ankylosing spondylitis • Multiple sclerosis • Psoriasis • Rheumatoid arthritis • Uveitis

Current and emerging strategies to inhibit type 2 inflammation in atopic dermatitis. *Dermatol Ther (Heidelb).* 2022 Jul;12(7):1501-33.

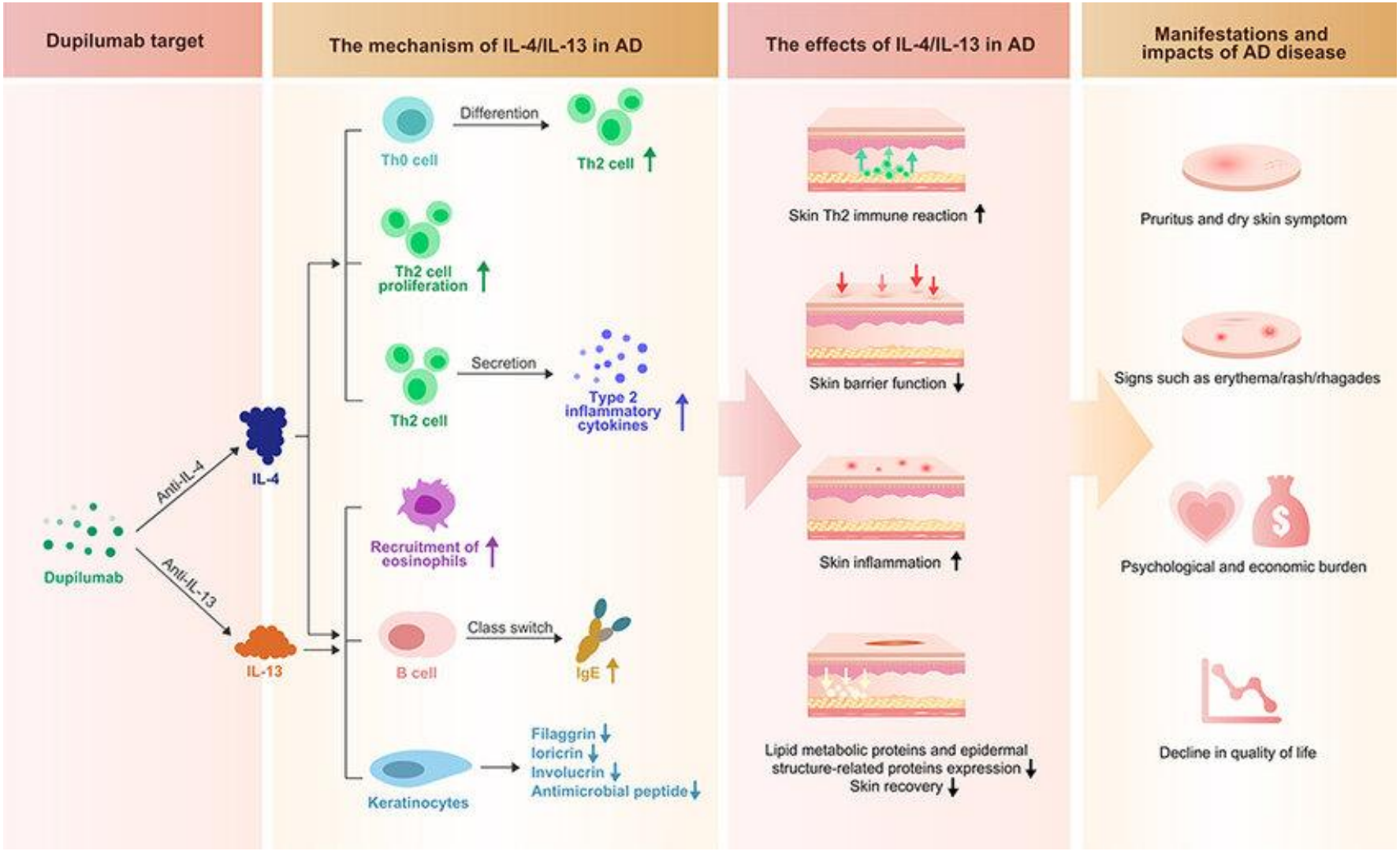
Appendix: Allergic Reaction Types

類型	I 型	II 型	III 型	IV 型
過敏反應類型 (Types)	立即型 Immediate	胞毒型 Cytotoxic	免疫複合體型 Immune Complex	細胞介導型 Cell-Mediated
作用機制 (Mechanism)	IgE 抗體與肥大細胞或嗜鹼性球結合，當再次接觸過敏原時，引發細胞脫顆粒，釋放組織胺等介質。	IgG 或 IgM 抗體結合到細胞或組織表面抗原，透過補體系統或吞噬細胞，導致目標細胞被破壞。	抗原與抗體（主要是 IgG）結合形成免疫複合體，沉積在血管壁或組織中活化補體系統並吸引嗜中性球，導致組織損傷。	記憶性 T 細胞（主要是 Th1）在再次接觸抗原時被活化，釋放細胞激素，引起巨噬細胞和 T 細胞的聚集與活化，導致組織損傷。反應通常在接觸後 24-72 小時後才發生。
主要參與者 (Key Players)	IgE 抗體、肥大細胞、嗜鹼性球、Th2 細胞	IgG/IgM 抗體、補體系統、吞噬細胞	免疫複合體 (IgG)、補體系統、嗜中性球	T 細胞、巨噬細胞、細胞激素
相關疾病 (Associated Diseases)	氣喘、過敏性鼻炎、蕁麻疹、食物過敏、藥物過敏	輸血反應、新生兒溶血症、某些自體免疫疾病 (如自體免疫溶血性貧血)	全身性紅斑狼瘡 (SLE)、類風濕性關節炎、血清病	接觸性皮膚炎 (如對鎳或毒藤過敏)、結核菌素反應、排斥反應 (器官移植)

Background - Dupilumab

- Dupilumab is a humanized monoclonal antibody directed against IL-4R-alpha subunit, inhibiting type 2 inflammation by **blocking IL-4 and IL-13 signaling**.
- For severe CRSwNP, Dupilumab reduces the need for surgery and oral corticosteroids.
- Side effects: Usually mild, including injection site erythema, conjunctivitis, & transient eosinophil ↑
  - => Relatively common during first month

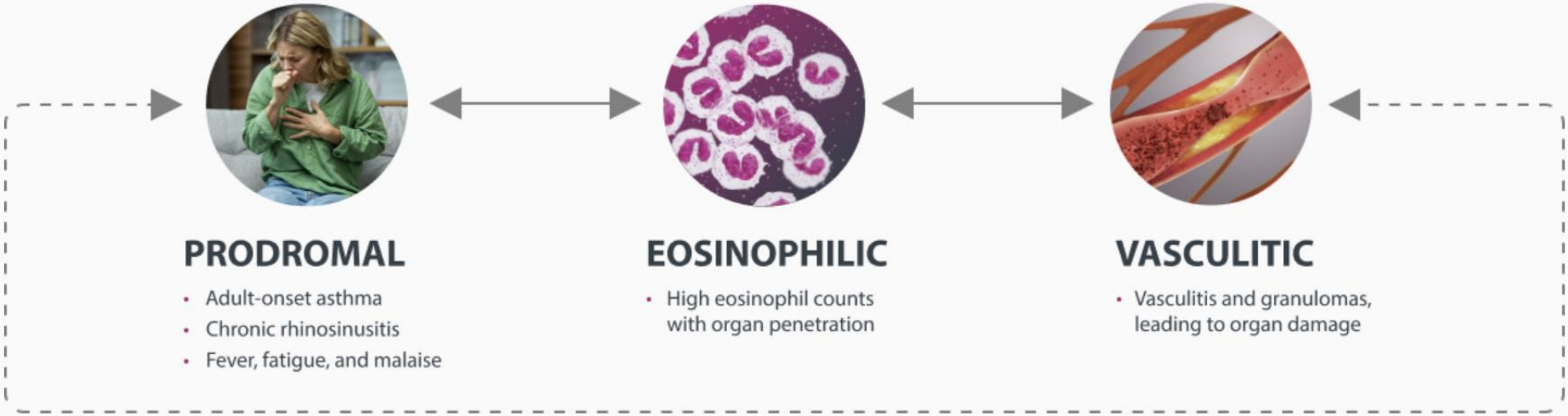
Dupilumab Inhibits Type 2 Inflammation



A review of dupilumab in the treatment of atopic dermatitis in infants and children. *Drug Des Devel Ther*. 2024 Mar;Volume 18:941–51.

Eosinophilic Granulomatosis with Polyangiitis (EGPA)

- Formerly called "Churg-Strauss syndrome"
- A multisystem disorder, characterized by chronic rhinosinusitis, asthma, and prominent peripheral blood eosinophilia.



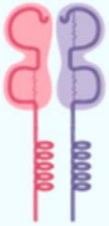
Clinical features and diagnosis of eosinophilic granulomatosis with polyangiitis (EGPA). *UptoDate.*

Main biological actors

Eosinophils

Anti-neutrophil cytoplasmic autoantibody (ANCA)

Genetic component



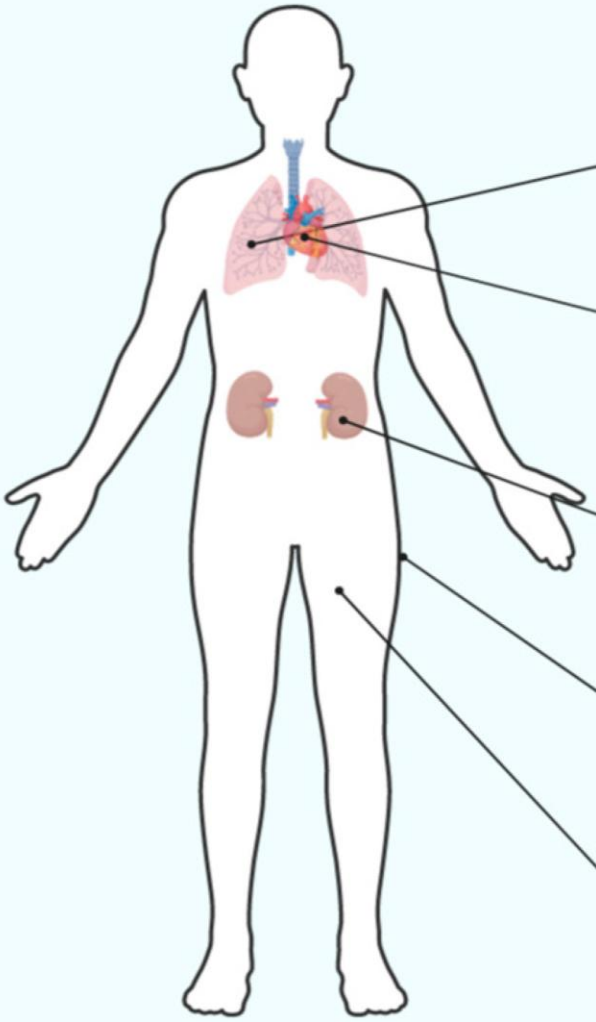
HLA class II

Other associated non-MHC genes

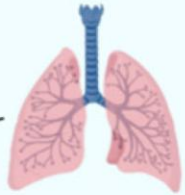
Environmental component

Pollutants

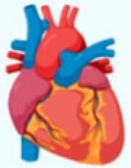
Occupational exposure



Organ involvement



Asthma
Rhinosinusitis
Pulmonary infiltrates



Myocarditis
Arterial and venous thromboembolic event
Coronary arteritis

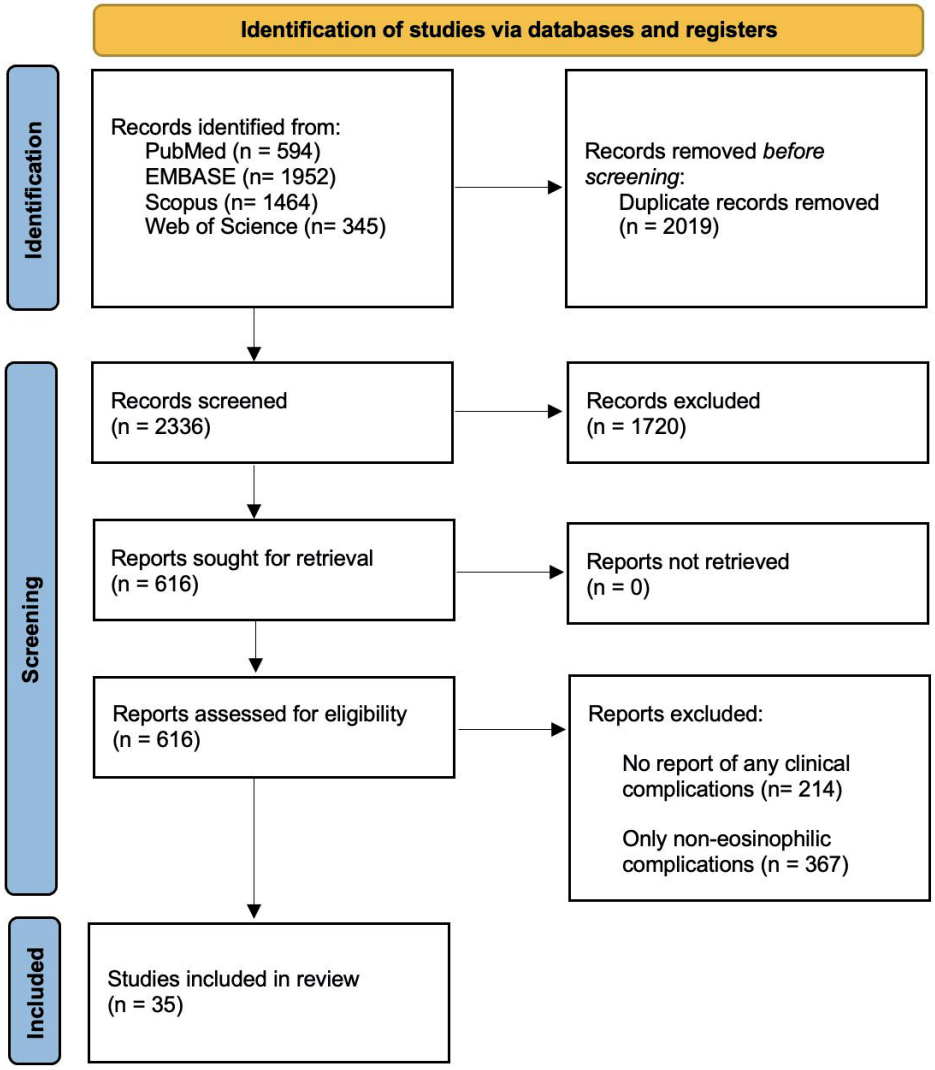
Glomerulonephritis
Tubulointerstitial nephritis

Purpura
Urticarial plaques
Papules

Peripheral neuropathies

Methods - Researches

- Search PubMed, EMBASE, Scopus and Web of Science in May 2024 using “Dupilumab AND (eosinophilia OR eosinophils OR hypereosinophilia OR "hypereosinophilic syndrome")”
- Final Included reports
  - 17 case reports
  - 6 RCTs
  - 7 case series
  - 5 cohort studies



Methods - Database

- To search for underreporting cases with adverse events
- This research used EudraVigilance database.
  - An E-system for analyzing information on suspected adverse reactions to medicines in the Europe.

Results - Basics

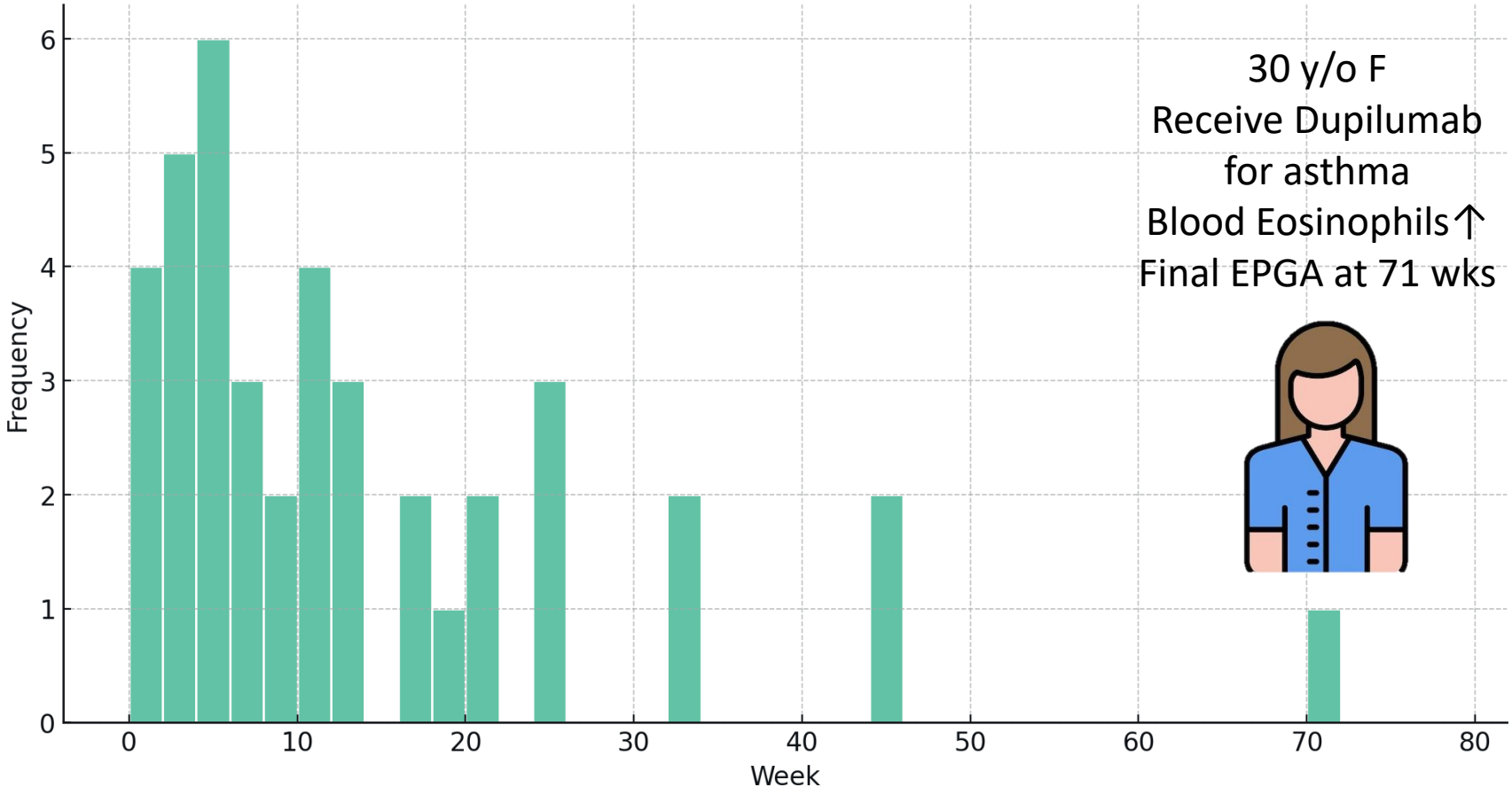
- 53 patients are included
- Median age: 56
- Sex: 73% female
- Initial symptoms:
  - 27 asthma patients
  - 12 asthma + CRSwNP
  - 10 CRSwNP
  - 4 AD
- 22 patients with med Hx of oral corticosteroids (OCS)

Results - Main Eosinophilic Complications

- Eosinophilic complications after Dupilumab therapy
  - EGPA: Appeared in 24 patients
  - Eosinophilic pneumonia: 15 patients
  - Hyper-eosinophilic syndrome: 6 patients
- Other isolated case reports
  - Eosinophilic myopericarditis
  - Eosinophilic pleuritis
  - Myositis
  - Non-EGPA eosinophilic vasculitis
  - Atrial fibrillation, stroke and anaphylaxis

Results - Onset Time

- The median eosinophil count when diagnosed was 6,380 cells/cumm.
- The eosinophilic complications developed after a median of 9 weeks.



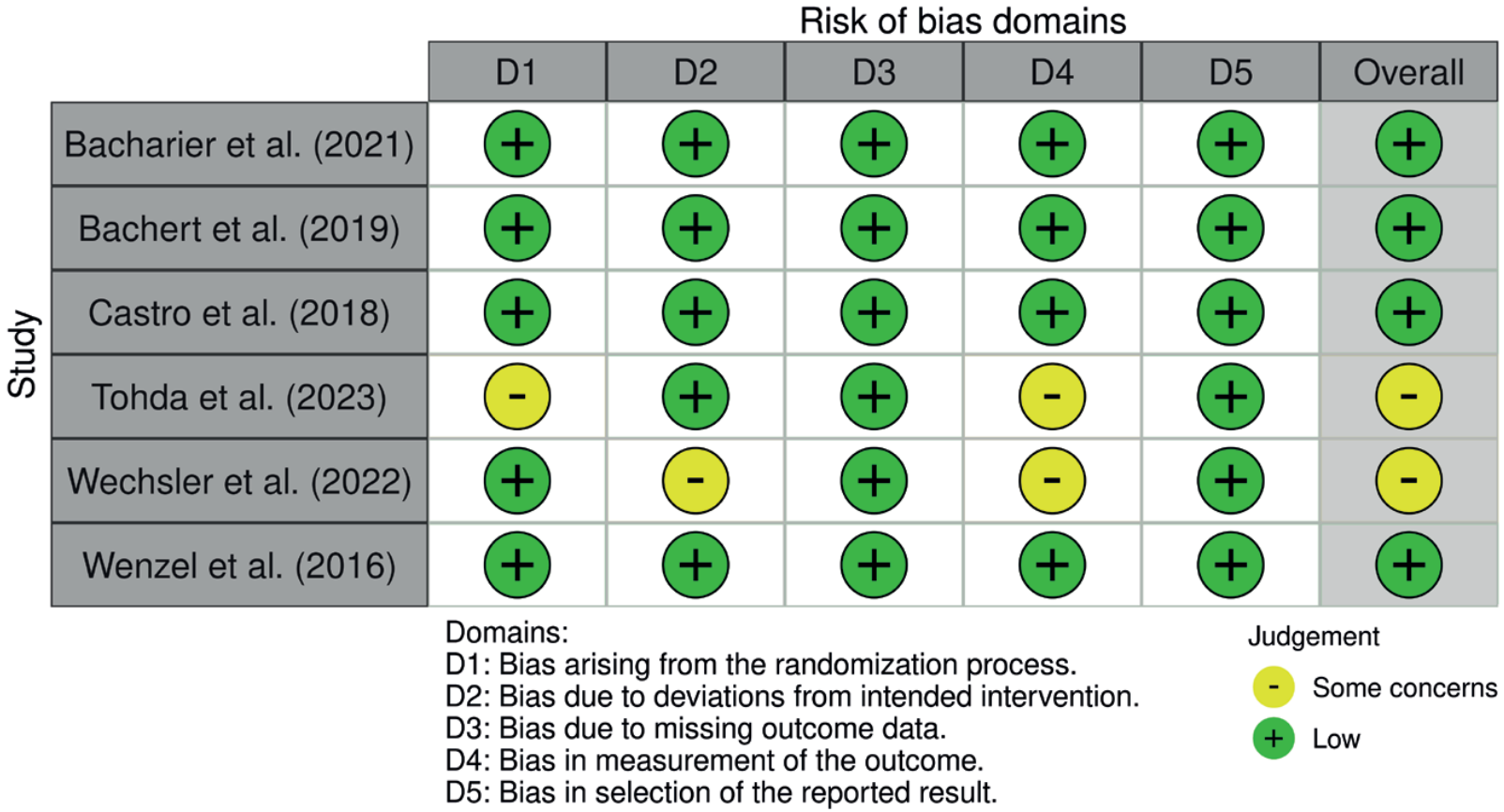
Results - Aftermath

- Dupilumab was discontinued in 89% cases
- Systemic corticosteroids started in 93% cases
  - 60% received OCS
  - 18% IV methylprednisolone
  - 5% IV/SC hydrocortisone
- Regimen switch
  - 13% switched to Mepolizumab
  - 13% switched to Benralizumab
- No any death was induced by eosinophilic complications.

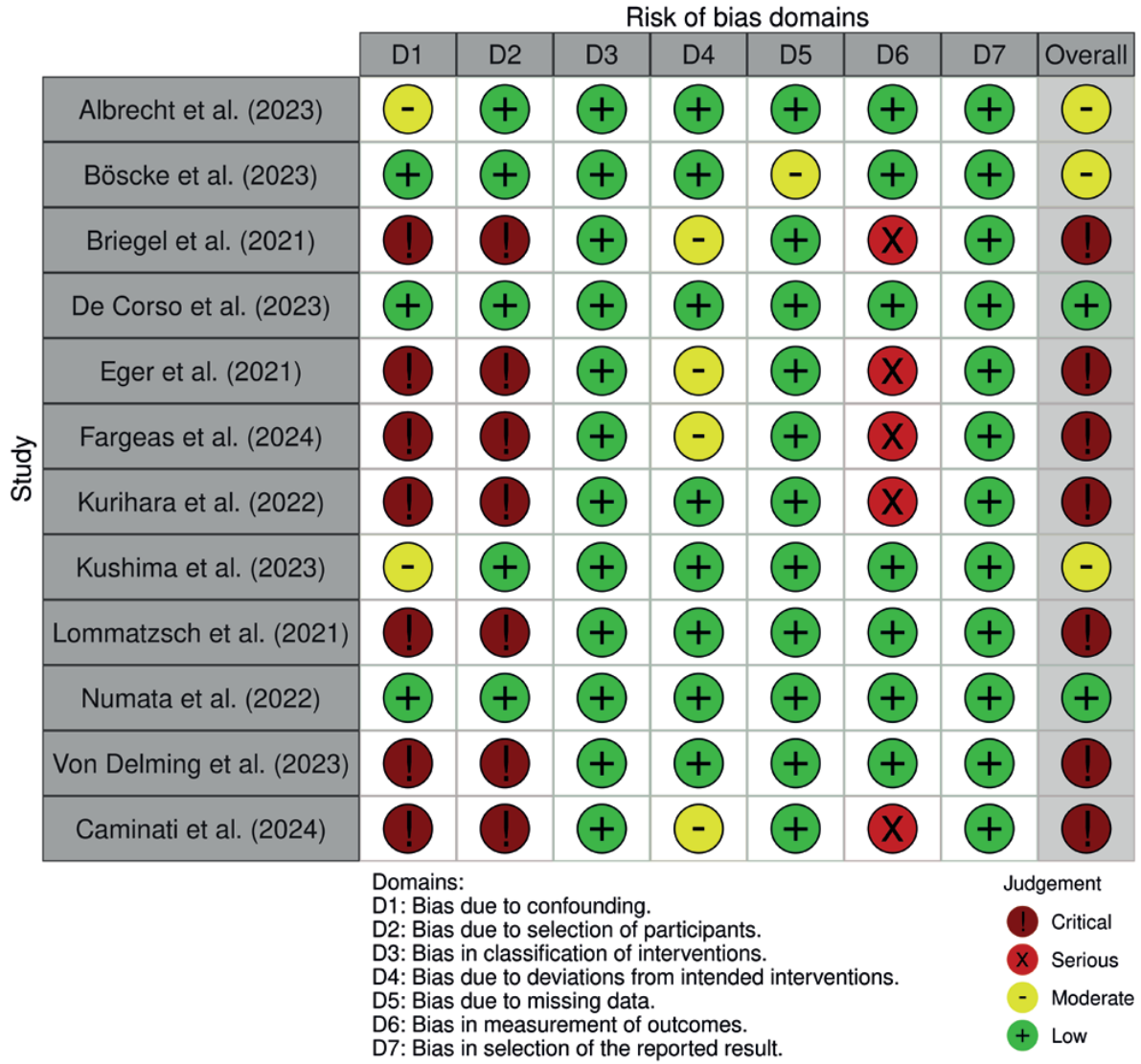
Results - EudraVigilance Database

- A total of 283 eosinophilic complication cases
  - EGPA: 144 cases
  - Eosinophilic pneumonia: 119 cases
  - Eosinophilic syndrome: 20 cases
- The complications resolved or are resolving **without sequelae in 82%** of the cases.
- Eosinophilic complications were fatal in only 2% of cases.

Results - Quality of Evidence



Results - Quality of Evidence



Discussion - Dupilumab

- Dupilumab has revolutionized the treatment of **type 2 inflammatory diseases** like asthma and atopic dermatitis.
- Dupilumab can cause **a temporary increase in blood eosinophil counts** during the initial treatment phase.
- The complications are extremely rare: Only 53 eosinophilic complication cases were identified within over 1 million patients have been treated.

Discussion - EGPA

- EGPA is the most common observed in eosinophilic complication cases.
- It is **unclear** if dupilumab causes EGPA or simply unmasks a pre-existing condition, especially in patients tapering off steroids.
- The majority of complications were reported in patients treated for asthma or CRSwNP.
- Complications were very rare in patients with AD.

Discussion

- Most complications occurred within the first 24 weeks of treatment.
- This timeline coincides with the transient peaks in eosinophil counts.
- Routine eosinophil monitoring after the first 52 weeks may not be necessary.
- Real-world data shows the incidence is exceptionally low.

Discussion - Limitations

- The study was limited by the risk of underreporting in medical literature.
- Searches in drug safety databases, such as EudraVigilance, found slightly more cases, but the overall number of complications remains extremely low.
- Although 2 deaths were reported in real-world data, the lack of patient details makes it impossible to determine a causal link.

Conclusion

- The review included various study types, so the evidence quality is uneven and should be interpreted with caution.
- A meta-analysis wasn't performed because of the high variability in study designs and patient populations.
- Despite these limitations, the study concludes that eosinophilic complications with dupilumab are extremely rare, which challenges the need for prolonged eosinophil monitoring.

Reference

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Thank You!