Interleukin-4/13 Versus Interleukin-5 Biologics and Risk of Asthma Exacerbations: A Real-World Cohort Study

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BACKGROUND

Asthma affected **~25 MILLION** Americans

5–10% have severe, uncontrolled disease

Leading cause of preventable hospitalizations, ED visits, and loss of lung function

- **Targeted Biologics:** Biologics including dupilumab (anti-IL-4Rα; blocks IL-4+IL-13), mepolizumab (anti-IL-5), and benralizumab (anti-IL-5Rα), are FDA-approved for the treatment of severe asthma in patients ≥6 years.
- **Prior Real-World Evidence:** No head-to-head RCT. Observational studies showed lower exacerbation rates with dupilumab vs IL-5 biologics, but data are largely limited to adults or adolescents, leaving a critical gap in other age groups.
- **Objective:** To compare the risk of asthma exacerbations between IL-4/13 vs IL-5 pathway biologics among patients aged >=6 years old.

METHODS

- **Retrospective Cohort · Active-Comparator New-User Design**
- **Data Source:** Merative MarketScan® + Medicare Supplemental (Jan 2017 – Dec 2024).
- **Population:**
  - Patients ≥6 years with uncontrolled asthma defined as ICD-10 J45, J82.83 and ≥1 of the following criteria:
    - Prescribed High-dose ICS+LABA or Medium-dose ICS+LABA.
    - Had at least one inpatient visit due to asthma diagnosis.
    - Had ≥2 outpatients or ED visit with asthma diagnosis as primary diagnosis + systemic corticosteroid use (±7d to asthma diagnosis).
  - Initiated dupilumab (IL-4 biologic) or mepolizumab/benralizumab (IL-5 biologics).
  - ≥6 months continuous enrollment.
- **Exclusion Criteria:** Patients with biologics claims without asthma diagnosis or who used multiple biologics at the same day.
- **Primary Outcome:** Time to first asthma exacerbation defined as ED/hospitalization with asthma exacerbation diagnosis (primary or secondary diagnosis), or outpatient asthma visit + OCS burst (3-21 days supply) within 7 days.
- **Follow-up:** Index date = first biologic fill. Per-protocol: censored at medication discontinuation, switching, disenrollment or end of study.
- **PS Matching:** 1:1 matching (caliper = 0.01, nearest-neighbor without replacement).
- **Statistical Analysis:**
  - Cox proportional hazards model to estimate the hazard ratio (HR) and 95% confidence interval (CI) for exacerbation risk.
  - Kaplan-Meier curves using log-rank test.
  - Two sensitivity analyses: (1) primary asthma exacerbation diagnosis only; (2) ITT analysis excluding medication discontinuation from censoring criteria.

PRIMARY FINDING

34% LOWER RISK

of ASTHMA EXCERBATION

HR 0.66 (95% CI: 0.59 – 0.73)

IL-4/13 Biologic vs IL-5 Biologics

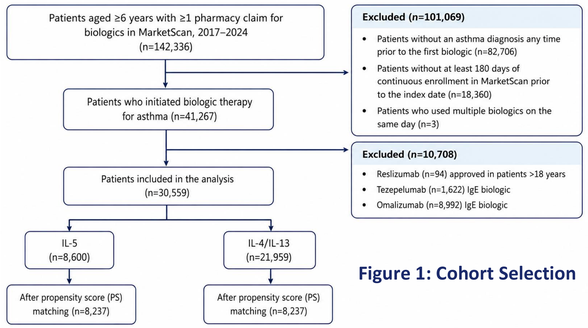

Figure 1: Cohort Selection

Table 1: Baseline Characteristics After PS Matching

Characteristic	Patients, n (%)		aSMD After PS Matching
	IL-5 (n=8,237)	IL-4/13 (n=8,237)	
Age, mean (SD), years	51.63 (15.10)	50.71 (15.61)	0.05
Sex: Female	5,218 (64.1)	5,176 (62.8)	0.03
US Region: South	3,910 (47.5)	3,736 (45.4)	0.02
Insurance Plan: PPO	4,300 (52.2)	4,176 (50.7)	0.01
Comorbidities			
• Respiratory infection	3,607 (43.8)	3,501 (42.5)	0.03
• Allergic conditions	5,148 (62.5)	5,385 (65.4)	0.06
• Chronic airways conditions	4,791 (58.2)	4,894 (59.4)	0.03
• Smoking	923 (11.2)	868 (10.5)	0.02
• GERD	2,102 (25.5)	1,961 (23.8)	0.04
• Metabolic conditions	3,235 (39.3)	3,126 (38.0)	0.03
Healthcare utilization			
• Inpatient with asthma	820 (10.0)	675 (8.2)	0.06
• >=2 outpatient or ED	5,669 (68.8)	5,453 (66.2)	0.06
Medications at baseline			
• High-dose ICS + LABA	6,042 (73.4)	6,046 (73.4)	0.00
• Medium-dose ICS+ LABA	2,309 (28.0)	2,402 (29.2)	0.03

All aSMD < 0.10 after matching

Abbreviations: ASMD, absolute standardized mean difference; **CI**, confidence interval; **ED**, emergency department; **F/U**, follow-up; **GERD**, gastroesophageal reflux disease; **HR**, hazard ratio; **ICS**, inhaled corticosteroid; **IL**, interleukin; **LABA**, long-acting beta-agonist; **PPO**, preferred provider organization; **PS**, propensity score; **PY**, person-years; **SD**, standard deviation.

RESULTS

Table 2: Overall Asthma Exacerbation: Primary Outcome

Biologics	Patients, n	Events, n	Mean F/U, days	Person-Years	Incidence Rate[a]	HR (95% CI)
IL-5 Biologics	8,237	1,279	318	7,164	**11.79**	*Reference*
IL-4/13 Biologic	8,237	661	261	5,884	**8.21**	**0.66 (0.59–0.73)**

Table 3: Asthma Exacerbation in Sensitivity Analyses

Biologics	Patients, n	Events, n	Mean F/U, days	Person-Years	Incidence Rate[a]	HR (95% CI)
Primary Diagnosis Only (Excluding Asthma Exacerbation Diagnosis as Secondary Diagnosis)						
IL-5 Biologics	8,237	817	319	7,193	**11.36**	*Reference*
IL-4/13 Biologic	8,237	473	261	5,890	**8.03**	**0.67 (0.59–0.75)**
Intention-to-Treat (Excluding Medication Discontinuation)						
IL-5 Biologics	8,237	1,402	571	12,876	**10.89**	*Reference*
IL-4/13 Biologic	8,237	835	488	10,000	**7.59**	**0.68 (0.62–0.74)**

[a] *Rate per 100 person-years*

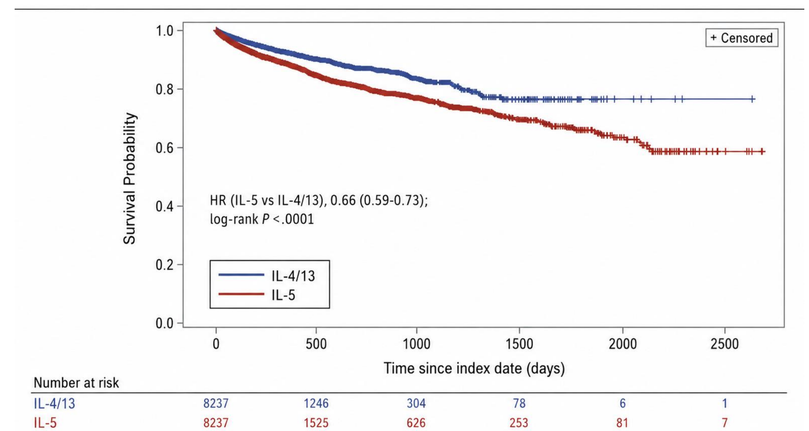

Figure 2: Kaplan-Meier Curves For Time to First Asthma Exacerbation

CONCLUSIONS

- **IL-4/13 biologic (dupilumab) was associated with a 34% lower risk of asthma exacerbation compared with IL-5 biologics in real-world patients ≥6 years old.**
- Findings support IL-4/13 blockade may offer superior exacerbation prevention and may inform treatment selection and future guideline updates.

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Disclosures and Acknowledgements
The authors have no conflict of interest to disclose.

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Full References

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