Research Protocol

Title: Comparative effectiveness and safety of omalizumab and dupilumab in children with asthma

Study Lead:
Chang Hoon Han, MD
Hamin Kim, MD
Seng Chan You, MD, PhD
Kyung Won Kim, MD, PhD

Contents

1. List of abbreviations

- IgE: Immunoglobulin E
- IL: Interleukin
- GINA: Global Initiative for Asthma
- EHR: Electrical health record
- OMOP-CDM: Observational Medical Outcomes Partnership Common Data Model

2. Abstract

This study aims to compare omalizumab and dupilumab, two of the most used biologic agents in the treatment of asthma. In cases of moderate-to-severe asthma where these drugs are indicated, this study will provide valuable evidence for guiding clinical decision-making, by conducting head-to-head comparison of these drugs on their effectiveness and safety.

3. Amendments and Updates

None

4. Rationale and Background

Biologic agents now account for more than 20% of the drugs annually approved by the US Food and Drug Administration (FDA), representing a rapidly expanding field. [1] Their efficacy has been demonstrated in diverse areas of medicine, including allergic diseases, where they are actively used to manage conditions such as moderate to severe-persistent asthma and chronic spontaneous urticaria. [2] Most of these agents are monoclonal antibodies that specifically target pathways involved in type 2 immune responses. [3] Biologic agents currently approved for treatment of asthma include omalizumab, which directly binds to free immunoglobulin E (IgE), mepolizumab, reslizumab, and benralizumab that targets interleukin-5 (IL-5) mediated signal, and dupilumab that binds to IL-4 receptor, blocking IL-4 and IL-13 mediated signals. [2, 3]

In Global Initiative for Asthma (GINA), biologics are considered as add-on therapy when step 5 treatment with other conventional agents including high-dose inhaled corticosteroids (ICS) and long-acting β2-agonist (LABA) fail to adequately control severe asthma, and are recommended only when there is evidence of elevated type 2 immune response markers. [4] Currently there is no clear distinction in the indications for different biologic agents, and a significant portion of patients who require biologics add-on therapy may fall under the indications of multiple biologic agents. [4, 5] While there have been attempts to provide guidance for treatment decisions based on phenotypic characterizations based on factors like blood eosinophil, lung function, and comorbid allergic diseases, there is limited evidence on comparative effectiveness and safety between biologics, limiting precise recommendations. [5]

Relatively recent studies on multiple biologics in asthma, marks steady advancement of our understanding on this area. However, many studies assess effectiveness and safety of each agent individually, and only few studies provide direct head-to-head comparisons. [6, 7] Akenroye et al. compared effectiveness of dupilumab, omalizumab and mepolizumab in adult asthma patients, and discovered superior reduction in exacerbations in dupilumab compared to the other agents. [8] Bleeker et al. compared effectiveness of dupilumab and omalizumab in asthma patients ≥ 12 years old and showed fewer exacerbations and systemic steroid prescriptions in dupilumab.[9] Further validation of these promising results using different databases with more subjects is warranted. Main goal of this study is to compare omalizumab and dupilumab, providing additional evidence to support the clinical decision-making process in asthma indicated with biologics treatment.

5. Aims and Objectives

This study is a cohort study which aims to:

I. Compare the effectiveness of omalizumab and dupilumab in pediatric asthma patients.
II. Compare the incidence of previously known side effects of omalizumab and dupilumab in pediatric asthma patients.

5.1. AIM 1. Comparative Effectiveness

- Determine and compare the incidence rate of asthma exacerbation in asthma patients on either omalizumab or dupilumab.

- Compare how much reduction of steroid use was achieved in asthma patients on either omalizumab or dupilumab.

5.2. AIM 2. Comparative Safety

- Determine and compare the incidence rate of previously known side effects of omalizumab and dupilumab, including eosinophilia, helminth infection, anaphylaxis, and conjunctivitis.

6. Research Methods

6.1. Study Design

This is a retrospective cohort study, comparing effectiveness outcomes and side effect incidence. Data sources will be electronic health record (EHR) data in Observational Medical Outcomes Partnership Common Data Model (OMOP-CDM) format, across the OHDSI network.

6.2. Study Population

6.2.1. Study Population for Comparison of Incidence Outcomes

The primary study population includes patients under the age of 18 diagnosed with asthma, either administered with omalizumab or dupilumab. Additionally, a secondary analysis will be done to include patients of all ages diagnosed with asthma.

The target group consists of patients who were initiated with omalizumab and who meet the criteria below. The comparator group consists of patients who were initiated with dupilumab and who meet the criteria below.

As primary analysis, intention-to-treat design will be applied to derive 1-year outcomes.
As sensitivity analysis, on-treatment design will be applied. The cohort exit rule described below will be applied.

Index rule defining the index date:

- First exposure to one of the agents of interest from 2018-11-01 and after.
- Under the age of 18 at the index date.
- With continuous observation of at least 180 days before the event index date.

Inclusion rules based on the index date:

- At least 1 occurrence of asthma between 30 days before and 7 days after the index date.
- None of exposure to the drug of the other group in the observation period before the index date.

Exit rules defining the cohort end date (on-treatment):

- Event will persist until end of a continuous drug exposure of interest.
- Allowance for 60-day gaps between exposure records of the drug of interest.
- Add 30 days to the end of the last exposure record as an additional period of surveillance.
- Censored with an exposure of the drug of the other group.

Table 1 Asthma Concept Set Definitions

Concept ID	Concept Name	Domain	Excluded	Descendant	Mapped
317009	Asthma	Condition	FALSE	TRUE	FALSE
4308356	Asthma finding	Condition	FALSE	TRUE	FALSE
4279553	Eosinophilic asthma	Condition	FALSE	TRUE	FALSE
4077802	Asthma monitoring	Observation	FALSE	TRUE	FALSE
46287068	At risk of severe asthma exacerbation	Condition	FALSE	FALSE	FALSE

6.2.2. Treatments of Interest

6.2.2.1. Target Drug: Omalizumab

Table 2 Omalizumab Concept Set Definitions

Concept ID	Concept Name	Domain	Excluded	Descendant	Mapped
302379	omalizumab	Drug	FALSE	TRUE	FALSE
21603362	omalizumab; parenteral	Drug	FALSE	TRUE	FALSE

6.2.2.2. Comparator Drug: Dupilumab

Table 3 Dupilumab Concept Set Definitions

Concept ID	Concept Name	Domain	Excluded	Descendant	Mapped
1593467	dupilumab	Drug	FALSE	TRUE	FALSE

6.2.3. Study Population for Steroid Dose Reduction Outcome

For this section of analysis, study population includes patients under the age of 18 diagnosed with asthma, either administered with omalizumab or dupilumab, with additional criteria of exposure to steroid within a certain period (3months or 6months) before index date. Likewise, a secondary analysis will be done to include patients of all ages diagnosed with asthma.

For 3-month total steroid dose reduction outcome

- Patients meeting criteria specified in 6.2.1. Study Population for Comparison of Incidence Outcomes
- At least 1 exposure of steroids specified in Table 4, 90 days before event index date.

For 6-month total steroid dose reduction outcome

- Patients meeting criteria specified in 6.2.1. Study Population for Comparison of Incidence Outcomes
- At least 1 exposure of steroids specified in Table 4, 180 days before event index date.

Table 4 Included Steroid Concepts

Concept ID	Concept Name	Domain	Class
1550557	prednisolone	Drug	Ingredient
1551099	prednisone	Drug	Ingredient
19086888	deflazacort	Drug	Ingredient
975125	hydrocortisone	Drug	Ingredient
1507705	cortisone	Drug	Ingredient
1506270	methylprednisolone	Drug	Ingredient
903963	triamcinolone	Drug	Ingredient
1518254	dexamethasone	Drug	Ingredient
920458	betamethasone	Drug	Ingredient

6.3. Outcomes

6.3.1. Primary Outcomes

6.3.1.1. Effectiveness Outcome – Asthma Exacerbation

Asthma exacerbation outcome is operationally defined as ER or inpatient visit due to asthma. The outcome cohort definition is as below.

Index rule defining the index date:

- A condition occurrence of asthma
- At least 1 occurrence of ER or inpatient visit, where the event starts before and ends after condition occurrence.

Table 5 ER or Inpatient Visit Concept Set Definition

Concept ID	Concept Name	Domain	Excluded	Descendant	Mapped

9201	Inpatient Visit	Condition	FALSE	TRUE	FALSE
9203	Emergency Room Visit	Condition	FALSE	TRUE	FALSE

6.3.1.2. Effectiveness Outcome – Steroid Dose Reduction

Steroid dose reduction outcome is defined as reduction in total steroid use, comparing certain time periods before and after index date. 3 months before and after index date for 3-month total steroid dose reduction outcome, and 6 months before and after index date for 6-month steroid dose reduction outcome.

Total cumulative dose of each steroid ingredient is calculated within the designated time periods. Total steroid use is then calculated from summation of total cumulative dose of all included agents, converted to prednisolone equivalent doses. Conversion is done with approximate equivalent dose based on relative glucocorticoid activity. [10, 11] The equation is as below.

(Total steroid use) = (Cumulative dose of prednisolone)
+ (Cumulative dose of prednisone)
+ (Cumulative dose of deflazacort × 5/7.5)
+ (Cumulative dose of hydrocortisone × 5/20)
+ (Cumulative dose of cortisone × 5/25)
+ (Cumulative dose of methylprednisolone × 5/4)
+ (Cumulative dose of triamcinolone × 5/4)
+ (Cumulative dose of dexamethasone × 5/0.75)
+ (Cumulative dose of betamethasone × 5/0.6)

Steroid dose reduction outcome is expressed using two different methods, as steroid dose percentage and steroid dose reduction groups, defined as below.

Steroid dose percentage:

- (Total steroid use after index date) / (Total steroid use before index date) × 100 (%)

Steroid dose reduction groups:

- Stop use
- Reduction of 75% or more
- Reduction of 50% or more, below 75%
- Reduction of 25% or more, below 50%
- Reduction below 25%
- No change or increased use

6.3.2. Secondary Outcomes

6.3.2.1. Safety Outcome – Eosinophilia

Three eosinophilia outcome cohorts based on severity are defined. (Eosinophil count above 500, 1500 and 3000 per microliter of blood)

Index rule defining the index date:

- A measurement occurrence of eosinophil greater than a designated value (500, 1500, and 3000)

Table 3 Eosinophil Concept Set Definition

Concept ID	Concept Name	Domain	Excluded	Descendant	Mapped
3013115	Eosinophils [#/volume] in Blood	Measurement	FALSE	FALSE	FALSE

6.3.2.2. Safety Outcome – Helminth Infection

Index rule defining the index date:

- A condition occurrence of helminth infection

Table 4 Helminth infection Concept Set Definition

Concept ID	Concept Name	Domain	Excluded	Descendant	Mapped
432251	Disease caused by parasite	Condition	FALSE	TRUE	FALSE
3012744	Ova and parasites identified in Specimen by Light microscopy	Measurement	FALSE	TRUE	FALSE

6.3.2.3. Safety Outcome – Anaphylaxis

Index rule defining the index date:

- A condition occurrence of anaphylaxis

Table 5 Anaphylaxis Concept Set Definition

Concept ID	Concept Name	Domain	Excluded	Descendant	Mapped
441202	Anaphylaxis	Condition	FALSE	TRUE	FALSE
4221182	Anaphylaxis due to substance	Condition	FALSE	FALSE	FALSE
4084168	Drug-induced anaphylaxis	Condition	FALSE	FALSE	FALSE
42536383	Anaphylactic shock	Condition	FALSE	FALSE	FALSE
4298385	Anaphylaxis management	Observation	FALSE	FALSE	FALSE

6.3.2.4. Safety Outcome – Conjunctivitis

Index rule defining the index date:

- A condition occurrence of conjunctivitis

Table 9 Conjunctivitis Concept Set Definition

Concept ID	Concept Name	Domain	Excluded	Descendant	Mapped
379019	Conjunctivitis	Condition	FALSE	TRUE	FALSE

6.3.3. Negative Control Outcomes

A total of 100 concepts were selected as negative controls that were not associated with both the target and comparator drugs and study outcomes.

Table 6 Negative controls outcomes

Concept ID	Concept Name	Concept ID	Concept Name
4115367	Wrist joint pain	438178	Postmastectomy lymphedema syndrome
4229262	Wilson's disease	4159151	Posthemorrhagic hydrocephalus
44813944	Vitamin D insufficiency	37311762	Posterior hypospadias
36684444	Vertebral joint pain	78830	Post-dysenteric arthropathy
140641	Verruca vulgaris	4091513	Passing flatus
4278836	Ulcer on tongue	438130	Opioid abuse
4293712	Traumatic oral ulceration	140648	Onychomycosis due to dermatophyte
437264	Tobacco dependence syndrome	136368	Non-toxic multinodular goiter
377575	Tinnitus	377572	Noise effects on inner ear
378427	Tear film insufficiency	4209423	Nicotine dependence
4051613	Sulcus vocalis of vocal cord	442136	Neoplasm of uncertain behavior of trachea
374053	Sudden hearing loss	76685	Myasthenia gravis
81151	Sprain of ankle	4101079	Middle ear finding
443172	Splinter of face, without major open wound	4128221	Microalbuminuric diabetic nephropathy

36714689	Somatic dysfunction of pubic region	4115107	Mass of female genital structure
36713918	Somatic dysfunction of lumbar region	4083487	Macular drusen
380706	Regular astigmatism	374912	Leukodystrophy
81634	Ptotic breast	37209383	Lesion of left ovary
439790	Psychalgia	438329	Late effect of motor vehicle accident
373478	Presbyopia	434203	Late effect of contusion
436676	Posttraumatic stress disorder	432593	Kwashiorkor
137820	Postoperative hypothyroidism	196168	Irregular periods
4002836	Postoperative hemorrhage	4335808	Injury of posterior cruciate ligament
4010333	Postmenopausal osteoporosis	444132	Injury of knee
4344500	Impingement syndrome of shoulder region	441669	Congenital anomaly of posterior segment of eye
374375	Impacted cerumen	432303	Cocaine abuse
436941	Hypervitaminosis A	4100822	Cobalamin deficiency
4182278	Hypermethioninemia	81378	Chondromalacia of patella
4012934	Homocystinuria	140842	Changes in skin texture
4012570	High risk sexual behavior	4213540	Cervical somatic dysfunction
4231770	Hereditary thrombophilia	434327	Cannabis abuse
37110444	Harmful pattern of use of nicotine	141055	Cancrum oris
433577	Hammer toe	73560	Calcaneal spur
4166231	Genetic predisposition	4108466	Burn of respiratory tract
40481632	Ganglion cyst	133655	Burn of forearm
4084433	Fracture of posterior malleolus	4128528	Asymptomatic proteinuria
259995	Foreign body in orifice	4140963	Anorectal anomaly
4110491	Fistula of nasal sinus	4103640	Amputated foot
4170770	Epidermoid cyst	45763909	Acute disruption of ankle syndesmosis
433111	Effects of hunger	77965	Acquired trigger finger
4237155	Eaton-Lambert syndrome	75911	Acquired hallux valgus
4339029	Double depressor palsy	44783954	Acid reflux
45757370	Disproportion of reconstructed breast	4092879	Absent kidney
4115402	Difficulty sleeping	4088290	Absence of breast
76786	Derangement of knee	4153106	Abscess of breast
78619	Contusion of knee	199192	Abrasion and/or friction burn of trunk without infection
4005447	Congenital pyloric stenosis	436409	Abnormal pupil
373489	Congenital nystagmus	434165	Abnormal cervical smear
4028847	Congenital duplication of stomach	375824	Abnormal auditory perception

7. Data Analysis Plan

7.1. Population Level Estimation

7.1.1. Covariates for Propensity scores

The types of baseline covariates used to fit the propensity score model will be:

- Demographics

    - Gender
    - Age groups (5-year bands)
    - Race
    - Ethnicity
    - Index Year/Month
- Condition Aggregation
    - In prior 30d or365d
- Drug Aggregation
    - In prior 30d or 365d
- Procedure
    - In prior 30d or 365d
- Device
    - In prior 30d or 365d
- Measurement
    - In prior 30d or 365d
    - Range Group in prior 365d
- Observation
    - In prior 30d or 365d

The concepts used in the definitions of the target and comparator cohorts are excluded from the propensity score model.

7.1.2. Data Analysis Plan

7.1.2.1. Definition of Time at Risk

Per analysis, time at risk is defined as below.

Primary analysis: Intention-to-treat (1 year)
- Time at risk start: Index date
- Time at risk end: Index date +365 day
- Minimum time at risk: 1day

Sensitivity analysis: On-treatment
- Time at risk start: Index date
- Time at risk end: Cohort end date
- Minimum time at risk: 1day

7.1.2.2. Statistical Model Specification

we compare the target cohort with the comparator cohort for the hazards of outcome during the time-at-risk by applying a Cox proportional hazards model. Incidence rates will be computed for each outcome in each exposure group.

Propensity score adjustment will be:
- PS stratification: The target cohort and comparator cohorts will be stratified into 5 stratums of the PS distribution.

Outcome model settings will be:
- Cox proportional hazards model will be used to estimate the risk of outcome between target and comparator cohorts.

7.1.2.3. Analysis to Perform

The following comparative analysis will be performed:
- One comparison:
    - New users of omalizumab with asthma (Target) vs. new users of dupilumab with asthma (Comparator)
- 2 populations:

- Age under 18
- All ages

- 7 outcomes:
  - Asthma exacerbation
  - Eosinophilia (Greater than 500/1500/3000)
  - Helminth infection
  - Anaphylaxis
  - Conjunctivitis
- 2 time-at-risk:
  - Intention-to-treat (1-year)
  - On-treatment
- One model: Cox-regression after PS stratification

7.1.3. Output

Output	Description
Propensity score distribution Plot	The propensity score distribution for both cohorts will be provided.
Propensity model	The propensity model will show the table that reports the covariates selected from propensity score models, with associated coefficients.
Covariate balance scatter plot	Covariate balance scatter plot will show the absolute standardized difference of mean before and after PS adjustment.
Attrition diagram	Attrition diagram will show the counts to meet the inclusion and exclusion criteria.
Kaplan-Meier plot	Kaplan-Meier plot will display the survival over time in both cohorts.
Population characteristics table	A table which lists some select population characteristics before and after PS adjustment will be created.

7.2. Steroid Dose Reduction Outcome

7.2.1. Statistical method

The difference between the target and the comparator will be shown for both as steroid dose percentage and steroid dose reduction groups. The statistical method is as follows.

For steroid dose percentage:

- Wilcoxon rank sum test.

For steroid dose reduction groups:

- Fisher's exact test will be used if any of the expected frequencies is <5.
- Chi-squared test will be used if all the expected frequencies are 5 or higher.

7.2.2. Output

Output	Description
Contingency table	A table which lists the number of patients in each steroid dose reduction group and the steroid dose percentage for both target and comparator group will be created. P-value from respective tests will also be displayed.

8. Strengths and Limitations of the Research Methods

8.1. Strength

- The new-user design can appropriately capture early events following treatment exposures while avoiding confounding from previous treatment effects.
- PS adjustment allows balancing on many potential confounders.

8.2. Limitations

- Even though many potential confounders will be included in this study, there may be residual bias due to unmeasured variables.
- Raw comparison will be done for steroid dose reduction outcome, and potential risk of confounding bias exists.

9. Protection of Human Subjects

In this study, we will use only de-identified data from CDM. Only the results of study will be aggregated, and the data will not identify individual subjects. The study was approved by the institutional review board of Yonsei University Health System, Severance Hospital. (No.4-2024-0232)

10. Plans for Disseminating and Communicating Study Results

At least one paper describing the study and its results will be written and submitted for publication to a peer-reviewed scientific journal.

11. Reference

1. de la Torre, B.G. and F. Albericio, *The Pharmaceutical Industry in 2021. An Analysis of FDA Drug Approvals from the Perspective of Molecules.* Molecules, 2022. **27**(3).
2. Sitek, A.N., J.T. Li, and T. Pongdee, *Risks and safety of biologics: A practical guide for allergists.* World Allergy Organ J, 2023. **16**(1): p. 100737.
3. Krings, J.G., et al., *Biologics for Severe Asthma: Treatment-Specific Effects Are Important in Choosing a Specific Agent.* J Allergy Clin Immunol Pract, 2019. **7**(5): p. 1379-1392.
4. *GINA Main Report 2024*.
5. Bacharier, L.B. and D.J. Jackson, *Biologics in the treatment of asthma in children and adolescents.* J Allergy Clin Immunol, 2023. **151**(3): p. 581-589.
6. Charles, D., et al., *Real-world efficacy of treatment with benralizumab, dupilumab, mepolizumab and reslizumab for severe asthma: A systematic review and meta-analysis.* Clin Exp Allergy, 2022. **52**(5): p. 616-627.
7. Park, S.Y., et al., *Real-World Effectiveness of Biologics in Patients With Severe Asthma: Analysis of the KoSAR.* Allergy Asthma Immunol Res, 2024. **16**(3): p. 253-266.
8. Akenroye, A.T., et al., *Comparative effectiveness of omalizumab, mepolizumab, and dupilumab in asthma: A target trial emulation.* J Allergy Clin Immunol, 2023. **151**(5): p. 1269-1276.
9. Bleecker, E., et al., *Comparative effectiveness of dupilumab and omalizumab on asthma exacerbations and systemic corticosteroid prescriptions: Real-world US ADVANTAGE study.* J Allergy Clin Immunol, 2024.
10. Liu, D., et al., *A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy.* Allergy Asthma Clin Immunol, 2013. **9**(1): p. 30.
11. Parente, L., *Deflazacort: therapeutic index, relative potency and equivalent doses versus other corticosteroids.* BMC Pharmacol Toxicol, 2017. **18**(1): p. 1.