Assessment and prediction of the effectiveness of anti-IL-5/IL5R inhibitors in a real-world setting: a two-step study

Catherine Lemiere MD, MSc

Lucie Blais PhD

CIUSSS du Nord de l'île de Montréal, Hôpital du Sacré-Cœur de Montréal

Université de Montréal

NCT06239441

February 15 2021

Scientific rationale

Asthma is a chronic respiratory disease affecting up to 8.4% of Canadians (1). While the majority of asthmatics are controlled with a low dose of inhaled corticosteroids (ICS), there are still approximately 10% of asthmatics who remain uncontrolled despite using high doses of an ICS with additional controllers. These patients are defined as severe asthmatics (2).

Over the past decade, it has become obvious that asthma is a heterogeneous disease that is composed of several phenotypes. The identification of those phenotypes has been associated with the development of biological therapies that specifically target antibodies, cytokines, and their receptors, such as immunoglobulin E, interleukin (IL) -5, and IL-5 receptor or IL-13/IL-4 receptor in the treatment of severe cases of asthma. Interleukin (IL)-5 plays a central role for eosinophil recruitment, activation, and survival. IL-5 and its receptor (IL-5R) have been targeted for developing antagonists against this cytokine or its receptor in the improvement of asthma control. There are three drugs targeting IL-5 or its receptor that have been developed to treat severe eosinophilic asthma: mepolizumab (Nucala™), reslizumab (Cinqair™)), and benralizumab (Fasenra™). Mepolizumab a humanized monoloclonal anti-IL-5 (IgG1) antibody was the first IL-5 antagonist to be commercialized in 2016 followed by reslizumab a humanized anti-IL-5 (IgG4/k) antibody. Benralizumab a humanized monoclonal antibody against interleukin 5 receptor α (IgG1κ) was commercialized in 2018 in the province of Quebec.

Anti-IL-5/IL5R inhibitors have been shown to decrease asthma exacerbations by approximately 50% (3, 4) and allow at least a 50% reduction in the doses of oral corticosteroids in cortico-dependent subjects(5, 6). Their efficacy has been mainly studied in clinical trials including selected populations. The effectiveness of anti-IL-5/IL5R inhibitors on the reduction of asthma exacerbations has rarely been assessed in a real-word setting where the characteristics of the patients receiving this medication differ substantially from the patients that were included in the clinical trials. Data from an Israeli tertiary clinic that followed 61 patients who had received mepolizumab for at least 3 months from 2016 to 2018(7) showed a large reduction of the annual asthma exacerbation rate before (3.14±2.3) and after treatment 0.85 ± 1.1 $p<0.001$).

However, it was unclear whether or not this study included smokers & ex smokers and the atopic status or the number of patients with a reversible airflow limitation were also not reported. In a

day-to-day practice, smokers and patients with a non-reversible airflow limitation or patients who are not optimally adherent to their asthma medication received mepolizumab, while at the same time were excluded or they represented a small proportion of the patients that were enrolled in the clinical trials.

The reduction of exacerbations has been shown to depend on the level of blood eosinophil counts. Better treatment effects were observed in patients showing high eosinophil counts (≥500 eosinophils/µL) compared to those with lower blood eosinophil counts. Although anti-IL-5/IL5R inhibitors have a very good response rate, some patients remain uncontrolled in spite of taking this medication(8, 9). Furthermore, although the addition of anti-IL-5/IL5R inhibitors allowed a 50% decrease in the dose of oral corticosteroids (OCS) in steroid-dependent patients, a fair proportion could not be completely weaned from prednisone (5, 6). Beside the baseline level of blood eosinophil counts(10), there is no other clear predictor of response to anti-IL-5/IL5R inhibitors.To our knowledge, no real-world study has ever tried to identify response predictors.

Therefore, it is essential to gather data from the real world to ensure that the response rate is at least as good as in the clinical trials and to identify predictors of response to therapy.

Hypothesis

The majority of patients receiving anti-IL-5/IL5R inhibitors will have at least a 50% decrease in their asthma exacerbations rate in a tertiary clinic specialized in the field of severe asthma.

The level of blood and sputum eosinophils will be the main response predictor to anti-IL-5/IL5R inhibitors in a tertiary clinic specialized in the field of asthma whereas the rate of exacerbation in the year prior to the initiation of anti-IL-5/IL5R inhibitors will be the main predictor of asthma exacerbations in a non-selected population of severe asthmatics in Quebec.

Primary Objectives

1. To assess and compare the response* to treatment before and after the initiation of anti-IL-5/IL5R inhibitors in patients followed in a tertiary asthma clinic from the Province of Quebec and in a non-selected population of asthmatic subjects covered by the *Régie de l'Assurance Maladie du Québec's (*RAMQ) public drug insurance plan or by a private drug insurance.

2. To assess the clinical response predictors to anti-IL-5/IL5R inhibitors in a cohort of severe asthmatics followed in tertiary care as well as in a non-selected population of asthmatic subjects covered by the RAMQ's public drug insurance plan *or by a private drug insurance.*

* Response to treatment will be defined by a reduction of asthma exacerbations of at least 50% ~~and~~ or a 50% or higher reduction of the OCS doses in steroid dependent patient compared to the year prior to treatment initiation.

Secondary objectives:

1. To assess the mean reduction of exacerbation in both cohorts.

2. To assess the adherence and persistence to treatment with anti-IL-5/IL5R inhibitors and ICS after treatment initiation with anti-IL-5/IL5R inhibitors..

Study populations.

A) A Tertiary asthma clinic cohort of patients 18 years and older who are followed at the outpatient asthma clinic of Sacre-Cœur Hospital and who have been treated with anti-IL-5/IL5R inhibitors between January 2016 and June 2020 and are included in the reMed database;

We will ensure that those patients had severe eosinophilic asthma inadequately controlled on high dose ICS plus additional controlled therapy and had a blood eosinophil count of 150 cells/µL on initiation or 300 cells/µL in the past 12 months and had either 2 or more significant asthma exacerbations in the past 12 months or were treated with daily oral steroids

B) A population-based cohort composed of two sub cohorts: a public sub cohort and a private sub cohort. All patients 18 years and older from the Province of Quebec who are covered by the RAMQ's public drug insurance plan that have been given anti-IL-5/IL5R inhibitors between January 2016 and June 2020 will constitute the public sub cohort. For the private sub cohort patient will selected from reMed, a drug claims database of a sample of Quebecers covered by a private drug insurance, by applying the same criteria.

.

In the province of Quebec the reimbursement criteria for mepolizumab are the following : severe eosinophilic asthma inadequately controlled on high dose ICS plus additional controlled therapy who have a blood eosinophil count of 150 cells/µL on initiation or 300 cells/µL in the past 12 months and had either two or more significant asthma exacerbations in the past 12 months or treatment with daily oral steroids whereas the reimbursement criteria for benralizumab are the following: severe eosinophilic asthma inadequately controlled on high dose ICS plus additional controlled therapy who have a blood eosinophil count of 300 cells/µL in the past 12 months and had either two or more significant asthma exacerbations in the past 12 months or treatment with daily oral steroids, or patients with severe eosinophilic asthma treated with oral corticosteroids for at least 3 months who have a blood eosinophil count of 150 cells/µL at treatment initiation Therefore, it is very likely that the patient enrolled in the study will comply with those criteria.

Target enrolment: Hundred (100) patients followed at the outpatient asthma clinic of the Sacre-Cœur Hospital who have been treated with anti-IL-5/IL5R inhibitors between January 2016 and June 2020.

We estimate that approximately 2000 patients have received anti-IL-5/IL5R inhibitors since 2016 in the Province of Quebec. Since 58% of patients are covered by a private drug insurance plan,

we estimate that we should be able to obtain data on approximately 1160 patients who have received anti-IL-5/IL5R inhibitors since 2016 and are covered by the public drug insurance. We will also be able to retrieve the data from 100 patients who are privately insured and received anti-IL-5/IL5R inhibitors from the reMed database.

Rate of enrolment N/A

Study start: Janaury 2021

Study end: December 2021

Study design

A retrospective pre-post anti-IL-5/IL5R inhibitors treatment cohort study using the RESP database and the hospital charts including patients with severe asthma followed at the *Hôpital du Sacré-Coeur de Montréal (*Tertiary asthma clinic cohort).

Another retrospective pre-post anti-IL-5/IL5R inhibitors treatment cohort selected from the Quebec health administrative databases and reMed database (Population-based cohort).

Cohort entry will be defined as the first prescription of anti-IL-5/IL5R inhibitors filled on or after January 1, 2016 for both cohorts.

Outcomes

Objective 1, primary outcome: Response to anti-IL-5/IL5R inhibitors, defined by a reduction of asthma exacerbations of at least 50% and a 50% or higher reduction of the OCS doses in steroid dependent patients in the year following the initiation of anti-IL-5/IL5R inhibitors compared to the year prior to treatment initiation, in the tertiary asthma clinic cohort and in the population-based cohort.

Objective 1, secondary outcomes: Exacerbation rates and OCS doses (for steroid-dependent patients) in the year preceding and following initiation of anti-IL-5/IL5R inhibitors in the tertiary asthma clinic cohort and in the population-based cohort.

Objective 2: Response to anti-IL-5/IL5R inhibitors in the tertiary asthma clinic cohort and in the population-based cohort in the year following initiation of anti-IL-5/IL5R inhibitors.

Potential Predictors

Potential clinical response predictors to anti-IL-5/IL5R inhibitors in the Tertiary asthma clinic cohort are: age, sex, atopy, body mass index, smoking habits, percent predicted FEV_1, asthma treatment prescribed, blood eosinophil count, and sputum eosinophil count at cohort entry.

Potential clinical response predictors to anti-IL-5/IL5R inhibitors in the Quebec population (Population-based cohort) are: age, sex, type of asthma treatment filled in the year before treatment initiation with anti-IL-5/IL5R inhibitors adherence to ICS in the year before and after treatment initiation with anti-IL-5/IL5R inhibitors, exacerbation rate in the year before treatment initiation with anti-IL-5/IL5R inhibitors, and socio economic status (welfare recipients).

Source of data

The RAMQ database is formed of three files containing information on the patients' characteristics, medical services and prescribed medications. The RAMQ Patient file contains the patient's healthcare insurance number (HCIN), which is a unique patient identifier, and information on age, sex, birth date, area of residence, type of drug insurance plan, and date of death, if relevant. This file covers all Quebec residents. The RAMQ Prescription Medications file contains the HCIN and claims data on prescriptions filled at community pharmacies; for example, name, dose, form, quantity of medication dispensed, date & duration of the prescription, cost of medications, as well as the identification and the specialty of the prescribing physician for Quebec residents covered under the RAMQ's Public Drug Insurance Plan, about 42% of the population; these include persons receiving social assistance, persons not covered by a private drug plan, and about 90% of elderly. This file also contains the dates of coverage under the RAMQ's Public Drug Insurance Plan. The RAMQ Medical Services file contains the HCIN and claims data on medical services dispensed on a fee for service to all residents of Quebec in hospitals, emergency departments (ED) or medical clinics. Physicians are reimbursed through RAMQ by submitting claims for medical services provided. This file contains the date of service, where the service was dispensed, one diagnosis coded with ICD-9, medical procedures provided,

cost of the service, as well as, specialty and identification of the treating physician. These databases can be linked between one and another using the HCIN.

The MED-ECHO database contains information on all admissions to acute care hospitals in Quebec. It contains the HCIN, the date of admission, length of stay, and diagnoses coded with ICD-9/ICD-10 codes; admission and principal & secondary diagnoses. The RAMQ and MED-ECHO databases can also be linked using the HCIN.

The reMed database contains data on medications dispensed in community pharmacies to a sample of patients with private drug insurance. The reMed contains the HCIN, the private insurance policy number (PIPN), the type of insurance plan (co-payment, annual premium, and so on), the name, dose formulation and quantity of the medication dispensed, the date the medication was dispensed, the pharmacy & the prescriber's encoded identifier, the cost of medications, and the amount reimbursed by the insurer. The drug related variables recorded in reMed are almost identical to the variables recorded in the RAMQ Prescription Medications file. The HCIN allows the linkage of the reMed to the RAMQ and MED-ECHO databases.

Methods

After having obtained the authorization from the research ethics committee of the CIUSSS du Nord-de-l'île-de-Montréal and from the director of Professional Services, all the charts of patients who received anti-IL-5/IL5R inhibitors at the tertiary asthma clinic of *the Hôpital du Sacré-Coeur de Montréal* will be reviewed.

A response to treatment will be defined by a 50% reduction in the number of asthma exacerbations in the year following the initiation of anti-IL-5/IL5R inhibitors compared to the year preceding the initiation of the treatment or a 50% decrease in the OCS doses for steroid dependent patients.

A functional response to treatment will also be assessed in the Tertiary asthma clinic cohort. An improvement of FEV_1 of 12 % and ≥200 ml will be considered as clinically significant.

Asthma exacerbations will be defined by a short treatment with systemic corticosteroids (less than 14 days), visit to the emergency department or hospitalization related to asthma. If two markers of an asthma exacerbation occurred with 14 days, they will be counted as only one exacerbation. This definition will be applied in the Tertiary asthma clinic cohort and the population-based cohort.

The potential predictors of response to treatment will be collected in the Quebec registry in respiratory health (RESP) database and or the medical charts: age (continuous), sex (women/ men), atopy (atopic/non atopic), body mass index (continuous), smoking habits (current or ex /never smokers)(never/ever/current), percent predicted FEV_1, asthma treatment (dose of ICS, dose of OCS if any), exacerbation rate in the year preceding treatment initiation, blood eosinophil count, and sputum eosinophil count.

The Quebec Registry in Respiratory Health (RESP) is a database originally built in 2010 by Dr Lucie Blais. This registry aims to store clinical and functional data in subjects with asthma and COPD followed at the *Hôpital du Sacré-Coeur de Montréal* or at the *Centre Hospitalier Universitaire de Sherbrooke*. The patients included in the database have also consented to have their clinical data matched to the *Régie de l'assurance médicale du Quebec* (RAMQ) and *Maintenance et exploitation des données pour l'étude de la clientèle hospitalière* (MED-ECHO) administrative databases and the reMed database on medications for patients with private health insurance plans which enables access to data on medical services, hospitalisations and medications dispensed by pharmacies. This databases allows us to collect the following variables: age, sex, area of residence (rural or urban), treatment (if insured with the RAMQ), co-morbidities, visits to the physician for asthma and all causes, visits to the emergency for asthma and any other medical issues, and hospitalization for asthma and any other medical issues.

This database allows us to assess the adherence to inhaled corticosteroids (ICS) by calculating the proportion of days covered (PDC) (11), a measure of adherence based on prescription claims data. The PDC is defined as the sum of the duration of all prescriptions of ICS filled over one year, divided by 365 days, expressed in percentages. The PDC will be estimated using prescription refill

data obtained from the RAMQ and reMed databases in the year preceding and following cohort entry.

Potential response predictors to treatment will also be collected in the RAMQ and reMed databases: age (continuous), sex (women/ men), type of asthma treatment (ICS, long-acting beta 2 agonists (LABA), Long-acting muscarinic antagonists (LAMA), Leukotriene-receptor antagonist (LTRA), omalizumab, or OCS if any), adherence to asthma treatment before and after cohort entry, comorbidities as measured by the Charlson score before and after cohort entry, exacerbation rate in the year preceding cohort entry, and area of residence (rural or urban) at cohort entry.

We shall require the authorization from *the Commission d'accès à information du Québec* to obtain the RAMQ and MED-ECHO data on healthcare utilization and medication for all subjects who have been diagnosed with asthma and who have been receiving anti-IL-5/IL5R inhibitors between January 2016 and June 2020; for example, subjects included in the tertiary asthma clinic cohort and the population-based cohort.

We will require from the RAMQ and MED-ECHO, the data on visits to the physicians, visits to the emergency departments, and hospitalizations for asthma and any other medical issues as well as the use of medication of all patients who have been diagnosed with asthma as defined by a validated operational definition(12) – 2 ambulatory visits for asthma or an hospitalization for asthma within the past 2 years a – in the year preceding the prescription of anti-IL-5/IL5R inhibitors and who have been receiving anti-IL-5/IL5R inhibitors from January 2016 to June 2020 in the Province of Quebec. We will request the data from January 2014 to June 2021.

Statistical analysis

We will estimate the proportion and confidence interval of patients' responder to anti-IL-5/IL5R inhibitors in the Tertiary asthma clinic cohort and the population-based cohort.

A logistic regression model will be used to identify the response predictors to anti-IL-5/IL5R inhibitors. Variable selection will be made with the Lasso selection procedure (13).

We will perform a Poisson regression model to compare the exacerbation rate in the year before and after the treatment initiation with anti-IL-5/IL5R inhibitors in the tertiary asthma clinic cohort and the population-based cohort. We will include all patients who received anti-IL-5/IL5R inhibitors in the analysis. The duration of follow-up will be taken into account using an offset in the Poisson regression model.

We will perform a linear regression model to compare the OCS doses in the year before and after the treatment initiation with anti-IL-5/IL5R inhibitors in the tertiary asthma clinic cohort and the population-based cohort.

Sample size and statistical power

To fulfill the primary objective

With 60 patients in the Tertiary asthma clinic cohort and an expected response rate of 50% we will have the power to identify 6 predictors (14). With 570 patients in the population-based cohort and an expected response rate of 50% we will have the power to identify more than 50 predictors (14).

With 60 patients in the tertiary asthma clinic cohort, an expected rate of 1.48 exacerbations per year per patient (3), and an alpha error of 5%, we will have a power of 80% to show a reduction of 50% in the rate of exacerbation (1 year post- anti-IL-5/IL5R inhibitors versus 1 year pre- anti-IL-5/IL5R inhibitors). With 570 patients in the population-based cohort and the same assumptions, we will have more than 90% power to show a reduction of 50% in the rate of exacerbation (1 year post- anti-IL-5/IL5R inhibitors versus 1 year pre- anti-IL-5/IL5R inhibitors).

Limitations

Fifty eight percent of Quebecers are covered by a private drug insurance. With reMed, we will be able to obtain this data for only a small sample of patients with a private drug insurance plan.

Perspective:

Up to date, the main prognostic factor identified in subjects treated with anti-IL5 is the level of eosinophilic inflammation. However, this factor has been identified in subjects enrolled in clinical trials. It is unknown whether, smoking, co-morbidities or adherence to ICS affects the response to anti-IL-5/IL5R inhibitors This study will be the first to answer this question in both a selected population followed in a tertiary asthma clinic and in a large population from Quebec.

Schedule of Activities

Study Procedures	**Estimated Date**
Ethic committee submission	November 2020
Submission to the *Commission d'accès à information du Québec/RAMQ*	December 2020
Clinical Data collection from RESP and hospital charts.	December 2020
First data analysis for clinical data And RAMQ data reception	March 2021
Submission of an abstract to the ATS	November 2021
Data Analysis	September 2021
Report and article writing	October 2021

References

1. Canada Go. Fast facts about asthma: Data compiled from the 2011 Survey on Living with Chronic Diseases in Canada

.

2. FitzGerald M, Lemiere C, Lougheed M, Ducharme F, Dell S, C R, et al. A Canadian Thoracic Society position statement. Can J Respir Crit Care Sleep Med. Can J Respir Crit Care Sleep Med 2017;1(4):199-221.

3. Farne HA, Wilson A, Powell C, Bax L, Milan SJ. Anti-IL5 therapies for asthma. Cochrane Database Syst Rev. 2017;9:CD010834.

4. FitzGerald JM, Bleecker ER, Nair P, Korn S, Ohta K, Lommatzsch M, et al. Benralizumab, an anti-interleukin-5 receptor alpha monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2016;388(10056):2128-41.
5. Bel EH, Wenzel SE, Thompson PJ, Prazma CM, Keene ON, Yancey SW, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. N Engl J Med. 2014;371(13):1189-97.
6. Nair P, Wenzel S, Rabe KF, Bourdin A, Lugogo NL, Kuna P, et al. Oral Glucocorticoid-Sparing Effect of Benralizumab in Severe Asthma. N Engl J Med. 2017;376(25):2448-58.
7. Pertzov B, Unterman A, Shtraichman O, Shitenberg D, Rosengarten D, Kramer MR. Efficacy and safety of mepolizumab in a real-world cohort of patients with severe eosinophilic asthma. J Asthma. 2019:1-6.
8. Cormier M, Chaboillez S, Lemiere C. Secondary loss of response to mepolizumab in severe eosinophilic asthma. J Allergy Clin Immunol Pract. 2019.
9. Cormier M, Cartier A. Recurrence of eosinophilic inflammation and worsening asthma symptoms between doses of benralizumab. J Allergy Clin Immunol Pract. 2020;8(10):3605-7.
10. Albers FC, Licskai C, Chanez P, Bratton DJ, Bradford ES, Yancey SW, et al. Baseline blood eosinophil count as a predictor of treatment response to the licensed dose of mepolizumab in severe eosinophilic asthma. Respir Med. 2019;159:105806.
11. Hess LM, Raebel MA, Conner DA, Malone DC. Measurement of adherence in pharmacy administrative databases: a proposal for standard definitions and preferred measures. Ann Pharmacother. 2006;40(7-8):1280-88.
12. Gershon AS, Wang C, Guan J, Vasilevska-Ristovska J, Cicutto L, To T. Identifying patients with physician-diagnosed asthma in health administrative databases. Can Respir J. 2009;16(6):183-8.
13. Tibshirani R. Regression shrinkage and selection via the lasso Journal of the Royal Statistical Society. 1996;58(B):267-88.
14. Peduzzi P, Concato J, Kemper E, Holford T, Feinstein A. A simulation study of the number of event per variable in logistic regression analysis. J Clin Epidemiol 1996;49(12):1373-9.