Research letter

Time on therapy and concomitant medication use of mepolizumab in Canada: A retrospective cohort study

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Time on therapy and concomitant medication use of mepolizumab in Canada: a retrospective cohort study

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Take home message:

About half of the patients who initiate therapy with mepolizumab discontinue treatment within the first or second year. Concomitant use of short-acting beta-2 agonists (SABA) and oral corticosteroids (OCS) dropped during mepolizumab use.
To the Editor,

Asthma is a chronic inflammatory condition that affects 3.8 million Canadians and nearly 65,000 acute asthma exacerbations occur each year [1-4]. Left untreated, asthma can lead to increasing mortality and morbidity [2, 5, 6]. Economically, the projected 20-year total costs (2014-2033) of sub-optimal asthma control in Canada are estimated to be $213 billion, of which the majority ($195 Billion) were productivity losses (presenteeism & absenteeism) [7].

In Canada and abroad, asthma control and the prevention of exacerbations is a treatment priority [3]. Current international guidelines advise the use of a combination inhaled corticosteroid (ICS) and long-acting beta agonist (LABA; specifically formoterol) for patients with mild disease (Global Initiative for Asthma [GINA] Steps 1-2), progressing to daily use of ICS-LABA according to the severity of the disease (GINA Step 3-5) and recommending the addition of tiotropium, anti-IgE, or anti-IL-5 biologics for patients with more severe disease (GINA Step 5)[5, 6].

Approximately 7% of patients with asthma are estimated to have severe uncontrolled disease, leading to substantial health impact as these patients contribute more than 60% of asthma-related healthcare costs [8]. Biologic therapies provide effective treatment options that may improve asthma control for these patients and Health Canada has approved several for the treatment of patients with severe asthma. Despite widespread clinical use and increasing availability, little is known about the real-world clinical outcomes related to continued therapeutic use for several of these biologic therapies.

At the time of this analysis, mepolizumab (NUCALA®, GlaxoSmithKline) has gained private and public market access across Canada and accumulated a cohort of patients with sufficient follow up to perform this study. We evaluated the real-world time to discontinuation of
mepolizumab using Canadian claims data, controlling for available patient factors (biologic treatment history, sex, age, region) and the concomitant use of short-acting beta-2 agonists (SABA) and oral corticosteroids (OCS).

Data were extracted from the IQVIA Private Drug Plan (PDP) dataset which contains de-identified patient-level data captured from 12 million active claimants (2012) across Canada, representing approximately 80% of the entire private market. All sources of data are actively managed, quality-controlled, and capture patient demographic characteristics, the specific drug dispensed, quantity dispensed, number of days supplied, and service date. This is a secondary analysis of anonymized administrative data and therefore ethics approval was not required.

All patients ≥ 18 years of age in the PDP database were eligible if they made at least one claim for mepolizumab between March 1, 2016 to December 20, 2019. Participants were excluded if their age or sex was missing and had fewer than 3 months drug plan history prior to initiation of therapy. Participants were followed until either mepolizumab discontinuation or end of follow-up period, at which point data were censored.

The primary outcome was time to treatment discontinuation, measured as the difference between date of final claim and date of first claim for mepolizumab. Date of final claim was defined as the latest chronological claim, with no further claims for mepolizumab for 90 days while maintaining drug plan status. Patients were censored if they had insufficient data to determine future claims (i.e. did not have 90 days of follow-up or drug plan activity after the final claim).

We captured age (years), sex (male or female), region of origin (British Columbia, Alberta, Prairies [Saskatchewan and Manitoba] Ontario, Quebec, Atlantic [New Brunswick, Nova Scotia,
Newfoundland, Prince Edward Island], and biologics treatment history (any claims for biologics in the 3-12 months prior to mepolizumab initiation).

Categorical data was summarised as count (percent) and continuous data were summarised as mean (standard deviation). We ran a Cox regression model to determine the effect of covariates on risk of discontinuation. We adjusted for age, sex, province, and treatment history with biologics and performed a sensitivity analysis based on year of initiation. Time to discontinuation was computed using the Kaplan-Meier method. We used one-way analysis of variance (ANOVA) to investigate the difference in the average proportion of people with claims made before, during and after mepolizumab use. Differences between these three periods were tested accounting for multiple comparisons using the Games-Howell procedure.

Data were available for 1,441 patients. The mean age (standard deviation [SD]) was 52 (11.2) years. Close to half of the participants were female (55.2%). Mean (SD) follow-up time was 11.6 (9.5) months (Median [quartile 1; quartile 3] = 9[4,17]). Almost half were from the province Ontario (683/47.4%) and 13% (196) had a prior history of treatment with biologics.

At 12 months post-treatment initiation, 40.3% of patients discontinued treatment with mepolizumab (95% CI: 37.3%-43.1%), increasing to 57.6% (54.0-60.9%) at 24 months. The mean (SD) time to discontinuation was 21.5 (0.5) months (Median [quartile 1; quartile 3] = 19 [17,22]). See figure 1 (panel A). Males were less likely to discontinue treatment than females (adjusted Hazard Ratio [aHR] 1.18; 95 confidence interval [CI] 1.01-1.39; p=0.047). Monthly utilization of SABA and OCS are shown in figure 1 (Panel B), suggesting decreased use of OCS or SABA while on mepolizumab in line with previous trials.
In this cohort of adult Canadians with severe asthma, we found that 40.1% and 54.6% of patients had discontinued mepolizumab treatment at 12 and 24 months, respectively. Males were more likely to discontinue than females. The use of SABA or OCS significantly decreased relative to the pre-treatment periods, but the magnitude of this benefit was not sustained following discontinuation (figure 1, panel B), in line with results from other studies [9,10].

To the best of our knowledge, this is the first report on real-world use of mepolizumab in the Canadian setting. In Canada, treatment with mepolizumab requires special access authorization with rigid criteria for initial and continued reimbursement. Therefore, discontinuation rates within this cohort are a relevant outcome for payers interested in system efficiency and therapeutic value and for physicians who may see this as a surrogate for treatment response [9,10]. These rates are also much higher that those in clinical trials, which noted ~14% discontinuation in the first year [11].

However, several important limitations are present given the nature of this database. Clinically, these data do not detail the reason for discontinuation and thus the direction (positive or negative) of the treatment response [9,10]. In addition, although we included only those patients who are actively using their private medical insurance, we must consider the impact of manufacturer-associated patient access programs (e.g. reimbursement bridging programs) relative to our use of the date of first reimbursement claim as an indication of treatment initiation. Nonetheless sensitivity analyses of a subset of patients selected from a period with high reimbursement coverage and low access support showed no difference in discontinuation from the overall cohort. Finally, utilization of SABA and OCS data were only available in aggregate form, which precludes our ability to investigate the relationship of these covariates on the discontinuation outcomes.
In summary, 40% of the patients that initiate therapy with mepolizumab discontinue treatment within the first year of treatment and 55% by the end of the second year of therapy. This level of discontinuation suggests substantial waste of time and resources given the cost of the drug and the clinician time involved in reimbursement navigation. Importantly for both patients and care providers, we cannot rule out clinical reasons for discontinuation including adverse events, treatment failure, suboptimal response, and patient preference [12]. Patients may also face challenges in securing time away from work for injections.

**Acknowledgements:**
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**References:**


4. CIHI. Emergency Department (ED) Visits: Volumes and Median Length of Stay by Triage Level, Visit Disposition, and Main Problem.


Figure 1: Survival plot for discontinuation and trends in average monthly claims for rescue medications

A. Survival curve for discontinuation

B. Trends in average monthly claims for rescue medications before, during and after use of mepolizumab

F(2, 45) = 93.54, p<0.001