Do inhaler adherence trajectories affect time to (biological) step-up treatment in patients with moderate to severe asthma?

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List of Abbreviations

Abbreviation or special term	Explanation
ATC	Anatomical Therapeutic Chemical Classification system
FDC	Fixed dose combination
GINA	Global Initiative for Asthma
ICS	Inhaled corticosteroids
LABA	Long-acting beta agonists
LAMA	Long-acting muscarinic antagonist
LTRA	Leukotriene Receptor Antagonist
OCS	Oral corticosteroids
PBS	Pharmaceutical Benefits Scheme
SABA	Short-acting beta agonist
SD	Standard Deviation

1. Background

International and national asthma treatment guidelines recommend a stepwise approach in the treatment of asthma. The Global Initiative for Asthma (GINA) distinguishes five steps of asthma as depicted in figure 1[1]. In steps 1-4, inhaled corticosteroids (ICS) and long-acting beta agonists (LABA) could be considered, which are relatively affordable and safe. In case patients show insufficient response to step 4 treatment (medium/high ICS/LABA), physicians may prescribe step-up therapies, such as biological treatment (anti-IgE, anti-IL-5), long-acting muscarinic antagonists or low-dose oral corticosteroids in GINA step 5. Contrary to step-up treatments within steps 1-4, which are generally safe and affordable, GINA step 5 treatment results in either more expensive (biological) or less safe (oral corticosteroids) options. As such, the GINA recommendation that step-up to these treatments should only occur after checking adherence first is of particular relevance when considering moving to step 5 treatment.

It is unknown whether people that are adherent to their step 4 medications, as objectively measured using their pharmacy dispensing records, have longer time to step-up treatment (to GINA step 5). In addition to adherence, other characteristics, such as disease severity, specific comorbidities (e.g. allergic rhinitis), beneficiary status, pharmacy and prescriber, may lead to different times to step-up treatment.

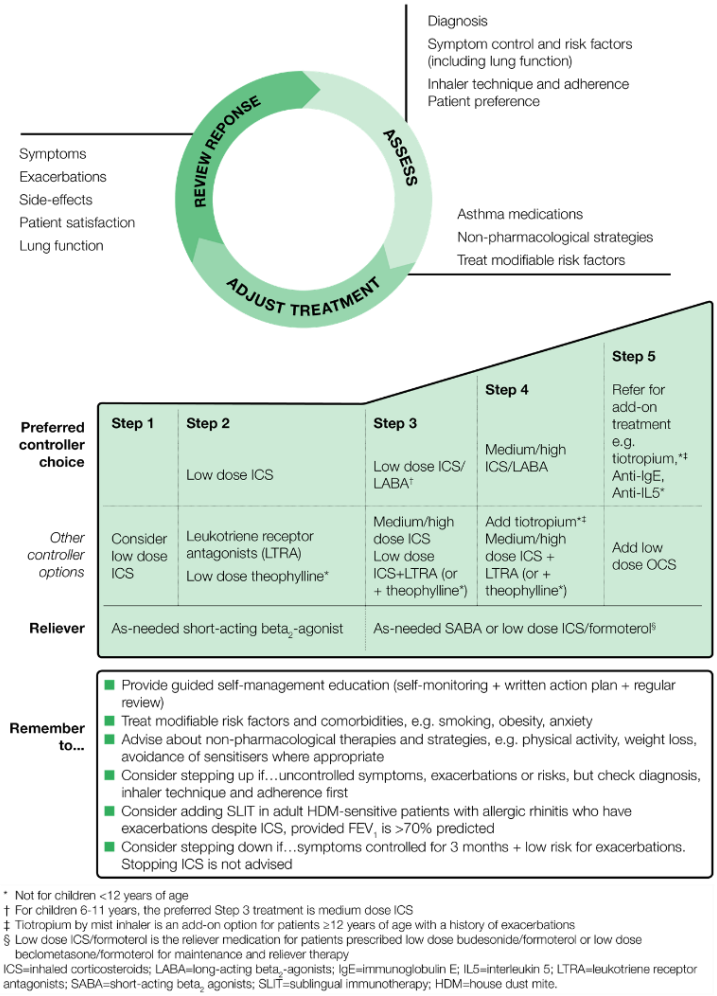

Figure 1: GINA asthma treatment algorithm

2. Objectives

2.1 Primary objective

The primary objective is to assess the impact of different inhaler adherence trajectories on the time to GINA step 5 treatment in patients initiating asthma maintenance treatment with inhaled corticosteroids (ICS) + long-acting beta agonists (LABA) in fixed dose combinations (FDC).

2.2 Secondary objective

The secondary objective is to identify other clinical and demographic predictors for step-up treatment. Analyses will be performed separately for those starting on different ICS/LABA FDC.

3. Study Design

This is an inception cohort study of patients with asthma who are new users of ICS/LABA FDC and represented in the 10% random sample of the Pharmaceutical Benefits Scheme (PBS) database. People with an index dispensing for these medications during the study period (July 2013 to June 2017 with 12-month look-back period) will be included. If the sample size is too small, we might use data from 2006 onwards.

A new user of ICS/LABA FDC is defined as an individual filling an ICS/LABA FDC prescription with no issued/dispensed prescriptions of that medicine class during the preceding year. Given some asthma patients have only intermittent use of ICS/LABA for seasonal asthma, the 1-year look back period might still include some intermittent users. Therefore, an initial comparison with a 2-year look back period will be performed and baseline characteristics compared to the 1-year look back period.

The date of the first filled prescription of the ICS/LABA FDC during the study period will be denoted the *index date*. Patients will be followed for 1 year from index date to estimate their 1-year ICS/LABA FDC adherence trajectory. Subsequently, the follow-up lasts until the earliest of: GINA step 5 medication started, death, or the end of the study period (August 2018).

Baseline characteristics including demographic and clinical characteristics will be captured for patients in the year before the index date.

An overview of the study design is presented in Figure 2.

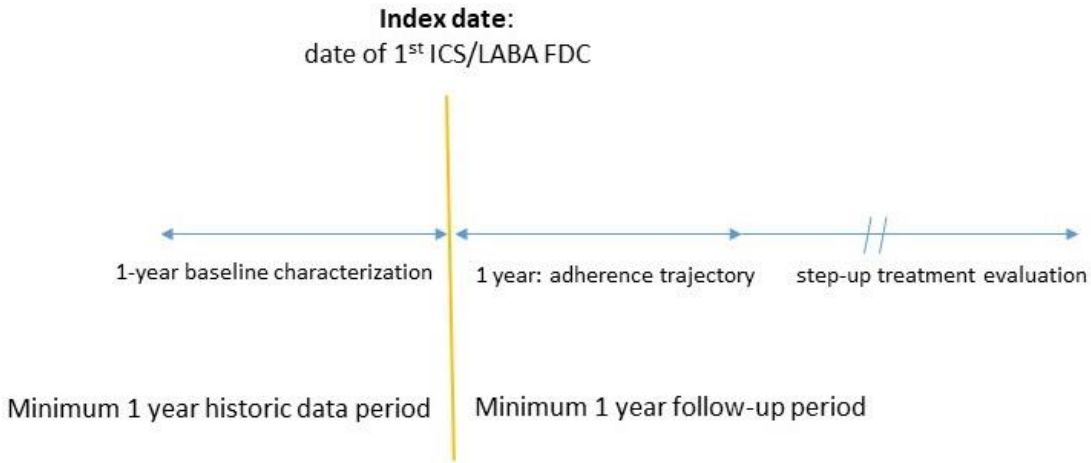

Figure 2: Overview of study design

4. Study population

4.1 Inclusion criteria

Inclusion criteria are:

- New user with a dispensed prescription of an ICS/LABA FDC product (defined as no dispensings of ICS/LABA FDC during the preceding 1 year)
- At least one year of follow-up data available after the index date
- At least one more ICS/LABA FDC dispensing (excluding index ICS/LABA FDC prescription) within one year after prescription at index date
- ≥ 12 years and <45 years old at index date[2,3]
- At least 2 other respiratory dispensings[4] (not being ICS/LABA FDC or GINA step 5 treatments) in the year before index date (i.e. any dispensings of single short-acting beta agonists (R03AC02, R03AC03, R03AK04, R03CC02, R03CC03), short-acting muscarinic antagonists (R03BB01), inhaled corticosteroids (R03BA), cromones (R03BC), xanthines (R03DA), or leukotriene antagonists (R03DC))

Interpretation of the inclusion criteria can be modified depending on the structure of data and availability the PBS database

4.2 Exclusion criteria

Exclusion criteria are:

- Patients <12 years and ≥45 years old at index date
- Patients with use of LABA (R03AC12, R03AC13, R03AC18) 1 year before or after index date
- Patients with use of GINA step 5 (i.e. (1): LAMA: R03BB04, R03BB05, R03BB06, R03BB07; (2) 1mg or 5mg prednisone or prednisolone: H02AB06, H02AB07 or (3): biologicals: R03DX05, R03DX09, R03DX10), 1 year before index date to 1 year after index date.

Interpretation of the exclusion criteria can be modified depending on the structure and availability of PBS data.

5. Definitions

5.1 Index date and index medication

The index date is defined as a date fulfilling the new user criteria regarding filled prescription of ICS/LABA FDC covered by PBS* (http://www.pbs.gov.au/browse/body-system?depth=4&codes=r03ak#r03ak) during the study period.

*The index medication includes the class ICS/LABA FDC covered by PBS that consists of: fluticasone/salmeterol (R03AK06), budesonide/formoterol (R03AK07), flucticasone furoate/vilanterol (R03AK10) and fluticasone/formoterol (R03AK11)

Individuals with a previous filled prescription of this medicine class during the preceding year (i.e. 365 before the index date) are not regarded as new users.

5.2 Baseline

5.2.1 General demographics

- Age at index date (=year of index date-year of birth)
- Sex (male=1/female=0)
- Concessional status
- Prescriber of index date ICS/LABA FDC medication (GP/specialist/unknown)
- State where index medication dispensed (WA/SA/NT/ACT/QLD/NSW/VIC)

5.2.2 Asthma severity indicators

In year (365 days) before index date:

- Annual number of dispensings of 25mg prednisone or prednisolone (ATC codes: H02AB06 and H02AB07).
- Annual number of dispensings of antibiotics (ATC codes: J01AA (tetracyclines), J01C (beta lactams), J01DA (cefalosporins), J01FA (macrolides).
- Annual number of SABA prescriptions (ATC codes: R03AC02 and R03AC03)
- Annual influenza vaccination: yes/no (presence of ATC code: J07BB)

5.2.3 Comorbidities

- Asthma specific comorbidities defined as at least one prescription within 1 year before index date:
  - Allergic rhinitis (nasal antihistamine: R01AC; systemic antihistamine: R06AD02-R06AX27, R06AB04; nasal steroids: R01AD)
  - Eczema/nasal polyps (topical steroids: D07, ointment with an immunosuppressant: D11)
  - Cough (R05)
  - GERD (proton pump inhibitors and others: A02BA01–A02BX05)
  - Oral thrush (nystatin: A01AB11; amphotericin B: A01AB04, miconazole: A01AB09)
- Other *chronic* comorbidities, possibly affecting ICS use (diabetes/osteoporosis/glaucoma: long-term side effects of ICS/OCS; anxiety/depression: risk for non-adherence; IBS: other indication for OCS use), present in year before initiation (defined by proxy, as

specified below). Patients need to have at least two of these dispensings within 1 year before index date, with ATC codes based on previously used Rx proxies[5]:

- diabetes (A10AA01–A10BX99)
- osteoporosis (M05BA01–M05BB05, M05BX03, M05BX04, G03XC01, H05AA02)
- anxiety (N05BA01–N05BA12, N05BE01)
- depression (N06AA01–N06AG02, N06AX03–N06AX11, N06AX13–N06AX18, N06AX21–N06AX26)
- IBS (A07EC01–A07EC04, A07EA01–A07EA02, A07EA06, L04AA33)
- Glaucoma (S01EA01–S01EB03, S01EC03–S01EX99)

5.2.4 Medication

- Asthma medication used in year before index date defined as presence of at least one prescription of:
    - SABA (R03AC02, R03AC03, R03CC02, R03CC03)
    - SAMA (R03BB01)
    - SABA/SAMA (R03AK04)
    - ICS (R03BA)
    - Cromo (R03BC)
    - Xanthines (R03DA)
    - LTRA (R03DC)

5.3 Exposures

The exposure of interest is use of- and adherence to- ICS/LABA FDC. For all ICS/LABA FDC prescriptions in the specified patient cohort of initiators, the following data is requested:

- item_code,
- pharmacy_state,
- supp_date,
- presc_date,
- presc_id,
- derived_specialty,
- type of script,
- concessional_status,
- quantity dispensed,
- number of repeats,
- number of scripts,
- number of previous scripts supplied,
- streamline_authority_code.

Other information regarding the dispensed drug will be added by linking a pbs-item-drug-map to the dataset. The pbs-item-drug-map contains: item_code, drug_name, form/strength and atc5_code.

6. Study Variables

The following variables will be extracted or derived, depending on availability.

6.1 Demographics

Table 1. Patient level information

Variable	Definition
Gender	Male (1), female (0)
Age	Age at initiation of ICS/LABA FDC
Year of first R03 since 2006	Calendar year of the date of the first R03 prescription (since 2006)
Year of index date	Year of initiation of ICS/LABA FDC
Socioeconomic factors	Concessional status at index date (Yes/no)
Prescriber of index medication	Prescriber of first ICS/LABA FDC at index date (GP/specialist)
State	State where patient is living (WA/SA/NT/ACT/QLD/NSW/VIC)

6.2 Medications

Table 2. Specification of asthma drug classes available in PBS

Drug class	ATC code
ICS/LABA FDC	R03AK06, R03AK07, R03AK10, R03AK11
SABA	R03AC02, R03AC03, R03CC02, R03CC03
SAMA	R03BB01
ICS	R03BA01, R03BA02, R03BA05, R03BA08
LABA	R03AC12, R03AC13, R03AC18
LAMA	R03BB04, R03BB05, R03BB06, R03BB07
LTRA	R03DC03
XANTHINES	R03DA02, R03DA04, R03DA05
CROMO	R03BC01, R03BC03
BIOLOGICS	R03DX05, R03DX09, R03DX10
SABA/SAMA	R03AK04
LABA/LAMA	R03AL03, R03AL04, R03AL05, R03AL06
LABA/LAMA/ICS	R03AL08
OCS	H02AB06, H02AB07

Other codes might be available and can be added as needed.

7. Outcomes

7.1 Primary outcome

Time to first dispense for a GINA step 5 treatment. GINA step 5 is defined as any dispense of the following:

- LAMA (tiotropium [R03BB04], aclidinium [R03BB05], glycopyrronium [R03BB06], umeclidinium [R03BB07]; and/or
- 1mg or 5mg oral corticosteroids (OCS): prednisolone [H02AB06], prednisone [H02AB07]; and/or
- Biologicals: omalizumab [R03DX05], mepolizumab [R03DX09], benralizumab [R03DX10])

7.2 Secondary outcome(s)

Predictors for time to GINA step 5 treatment.

8. Analysis Methods

8.1 Descriptive Analyses

Baseline characteristics will be described using descriptive statistics. Categorical variables will be described by frequencies and percentages. Continuous variables will be described using mean (± standard deviation [SD]) for normally distributed data or median and interquartile range (IQR) for skewed distributions.

For the index ICS/LABA FDC group, the percentage breakdown of individual agents covered by PBS, i.e. fluticasone/salmeterol (R03AK06), budesonide/formoterol (R03AK07), fluticasone furoate/vilanterol (R03AK10) and fluticasone/formoterol (R03AK11) (both in terms of number of patients but also by total follow-up time).

8.2 Adherence trajectories

Adherence to ICS/LABA FDC will be calculated using trajectory modeling from index date until 1-year follow-up.
Trajectory: We will use dispensing dates to define medication use in each month of follow-up. Distinct trajectories will be identified using group-based trajectory modeling in SAS. Adherence trajectories will be based on adherence to any ICS/LABA FDC. As such, switching between any different ICS/LABA FDC (ATC codes R03AK06-R03AK12) is allowed and is not considered step-up or discontinuation. For each trajectory, frequencies of patients with similar trajectories will be presented.

8.3 Comparative Analyses

Event
The event of interest is step-up treatment to GINA step 5, defined as any dispense (no matter being it an add-on or a switch from ICS/LABA FDC) of:

- LAMA (tiotropium [R03BB04], aclidinium [R03BB05], glycopyrronium [R03BB06], umeclidinium [R03BB07]; and/or
- 1 or 5mg oral corticosteroids (OCS): prednisolone [H02AB06], prednisone [H02AB07]; and/or
- Biologicals: omalizumab [R03DX05], mepolizumab [R03DX09], benralizumab [R03DX10])

In descriptive analyses, total number of events (combined, and per subgroup of LAMA, OCS or biological) over the complete follow-up will be analyzed.

In incidence analyses, only the first episode of the event will be included. Person-time at risk for each patient will be the length of the index exposure episode, defined as the number of days from the day after the index prescription start date to the last day of follow-up. For each outcome of interest, the crude incidence rate in each index exposure group is the number of incident events divided by the total number of person-years at risk and will be expressed per 100 person-years with 95% confidence intervals.

The primary analysis is based on follow-up starting 365 days after index date. The first 365 days are only used for adherence characterization.

The incidence rates for the event will be compared between adherent (as defined by distinct trajectories in period between index date and index date+365 days) new initiators of the ICS/LABA FDC and non-adherent (as defined by distinct trajectories in period between index date and index date+365 days).

Time to step-up and its predictors
Hazard ratios for time to GINA step-5 treatment and corresponding 95% confidence intervals will be assessed using Cox proportional hazards models with exposure group as only covariate. In this hazard ratio, adherence to ICS/LABA FDC will be considered the exposure and time-to-GINA step 5 treatment the outcome. Covariates (e.g. patient demographics) will be added one-by-one to assess their impact on the outcome. In addition, Kaplan-Meier plots are also provided for each of outcomes analyzed.

8.4 Sensitivity analyses

Additional analyses in order to check the robustness of the results include the following.

1. Only including time to biological step-up treatment, patient is censored at first biological treatment
2. Only including time to low dose (1mg/5mg) OCS treatment, patient is censored at first low-dose OCS treatment
3. Include unlicensed (potential) GINA step 5 treatments in the time-to-step up definition: (1) chronic (>5 dispensings) macrolide dispenses of roxithromycin (J01FA06), erythromycin (J01FA01), and azithromycin (J01FA10); (2) montelukast (R03DC03); (3) ciclesonide (R03BA08)
4. For each step, analyze using the Cox model adjusted for baseline covariates.

8.5 Subgroup analyses

Analyses will also be performed within a number of pre-specified subgroups:

- Gender (male/female)
- By age groups (age at index date: 12-19 versus 20-29; 30-39; 40-44 years)
- With/without prior asthma-specific comorbidities (yes/no, see appendix Table 3)
- By different ICS/LABA FDC starting dose (low versus medium and high[6]) (Table 3)

Table 3: ICS dose strengths and PBS item codes (Jan 2019)

ICS/LABA FDC	Low	Medium	High
R03AK06	08430Q, 08517G	08431R, 08518H	08432T, 08519J
R03AK07	02867X, 02938P, 08796Y, 10024N, 10015D	02866W, 08625Y, 10018G, 11273H	08750M, 11301T
R03AK10	-	10199T, 11124L	10167D, 11129R
R03AK11	02827T	10007Q	10008R

- By different ICS/LABA FDC type (see appendix Table 4)
- With/without 2 or more oral short courses of OCS and/or antibiotics in baseline year
- Prescriber of ICS/LABA FDC index date medication (GP/specialist/other)
- Concessional status: yes/no
- Optional (only, if data from before 2012 are used): Index date after July 2012: yes/no

8.6 Missing data

Missing data will not be imputed for any of the baseline variables.

9. Appendix: Tables plan

Table 1. Baseline patient and clinical demographics (N=)

	Total
Number of patients (N)	
General characteristics	
Gender (N, % female)	
Age at index date, mean (sd)	
Calendar year of index date	
Before July 2012, N (%)	
After July 2012, N (%)	
Concessional status, % yes	
Prescriber of index medication (% GP)	
State (where patient lives, % per state)	
Asthma characteristics	
OCS 25 mg dispensings, mean (SD)	
≥2 25 mg OCS dispensings , N (%)	
Antibiotic courses, mean (SD)	
≥2 antibiotic dispensings, N (%)	
≥2 25 mg OCS and/or antibiotic disensings, N (%)	
Influenza vaccination: yes/no (N, %)	

Table 2. Baseline background asthma medications (N=)

N, %	**Total**
SABA	X (X.X)
SAMA	
ICS	
LTRA	
XAN	
CROMO	
SABA/SAMA	

Table 3. Baseline comorbidities (N=)

N, %	Total	Adherent	Non-adherent
Asthma specific			
Allergic rhinitis	X, (X.X)		
Eczema/nasal polyps			
Cough			
GERD			
Oral thrush			
Other chronic comorbidities			
Diabetes			
Osteoporosis			
Anxiety			
Depression			
Glaucoma			
IBS			

Table 4. Distribution of index medications

	Total (N)	Mean ICS dose (µg)	Adherent (N, %)	Non-adherent (N, %)
ICS/LABA FDC (N, %)				
Total				
Low dose ICS				
Medium dose ICS				
High dose ICS				
fluticasone/salmeterol				
budesonide/formoterol				
flucticasone furoate/vilanterol				
fluticasone/formoterol				

Table 5. Distribution of adherence trajectories (accompanied by visual adherence trajectory presented in Figure)

	Total	Considered proper adherence (yes/no)
Trajectory (N, %)		
1		
2		
3		
4		
5		
6		
7		

Table 6. Output from Cox regression models

	N	Events	Hazard ratio	95% CI	P-value	SE*
Step-up any, 1-year adherence, unadjusted						
Step-up any, 1-year adherence, adjusted						
Step-up OCS, 1-year adherence, unadjusted						
Step-up OCS, 1-year adherence, adjusted						
Step-up biologicals, 1-year adherence, unadjusted						
Step-up biologicals, 1-year adherence, adjusted						
Step-up any (incl unlicenced), 1-year adherence, unadjusted						
Step-up any (incl unlicenced), 1-year adherence, adjusted						

*SE is the standard error of the log(HR) estimate

Table 7. Sub-group analysis: Step up to any GINA step 5

	N	Events	Hazard ratio	95% CI	P-value	SE*
Male (ref: female)						
Age 20-29 (ref: 12-19)						
Age 30-39 (ref: 12-19)						
Age: 40-44 (ref: 12-19)						
Comorbidities yes (ref: no)						
Any asthma specific						
Any other comorbidity						
Medium/high dose ICS (ref: low dose)						
Prescriber specialist (ref: GP)						
Concessional status yes (ref: no)						
Index date after July 2012 (ref: before July 2012)						

*SE is the standard error of the log(HR) estimate

10. References

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