Characterization of biologic initiation in a real-world severe asthma cohort with high exposure to oral systemic steroids

Wenjia Chen, PhD[1]; Mohsen Sadatsafavi, MD, PhD[2]; Trung N. Tran, MD, PhD[3]; Ruth B. Murray, PhD[5]; Chong Boon Nigel Wong, B.Soc.Sci. (Hons)[1]; Nasloon Ali, PhD[4,5]; Cono Ariti, MSc[4,5]; Esther Garcia Gil, MD[6]; Anthony Newell, PhD[4,7]; Marianna Alacqua, MD, PhD[8]; Mona Al-Ahmad, MD, FRCPC[9]; Alan Altraja, MD, PhD[10]; Riyad Al-Lehebi, MD, FRCPC[11,12]; Mohit Bhutani, MD, FRCPC[13]; Leif Bjermer, MD, PhD[14]; Anne Sofie Bjerrum, MD, PhD[15]; Arnaud Bourdin, MD, PhD[16]; Lakmini Bulathsinhala, MPH[4,5]; Anna von Bülow, MD, PhD[17]; John Busby, PhD[18]; Giorgio Walter Canonica, MD[19,20]; Victoria Carter, BSc[4,5]; George C. Christoff, MD, PhD, MPH[21]; Borja G. Cosio, MD, PhD[22]; Richard W. Costello, MB, MD, FRCPI[23]; J. Mark FitzGerald, MD, FRCPC[24]; João A. Fonseca, MD, PhD[25]; Kwang Ha Yoo, MD, PhD[26]; Liam G. Heaney, MD[27]; Enrico Heffler, MD, PhD[19,20]; Mark Hew, MBBS, PhD, FRACP[28,29]; Ole Hilberg, MD, DMSc[30]; Flavia Hoyte, MD[31,32]; Takashi Iwanaga, MD, PhD[33]; David J. Jackson, MBBS, MRCP (UK), PhD[34,35]; Rupert C. Jones, MD[36]; Mariko Siyue Koh, MBBS, MRCP (UK), FCCP[37,38]; Piotr Kuna, MD, PhD[39]; Désirée Larenas-Linnemann, MD, FAAAAI, Dist.Intl.FACAAI[40]; Sverre Lehmann, MD, PhD[41]; Lauri A. Lehtimäki, MD, PhD[42,43]; Juntao Lyu, PhD[4,7]; Bassam Mahboub, MD[44,45]; Jorge Maspero, PhD[46,47]; Andrew N. Menzies-Gow, PhD, FRCP[48]; Concetta Sirena, PhD[49]; Nikolaos G. Papadopoulos, MD, PhD, FRCP[50,51]; Andriana I. Papaioannou, MD, PhD[52]; Luis Perez-de-Llano, MD, PhD[53,54]; Diahn-Warng Perng Steve, MD, PhD[55,56]; Matthew Peters, MD, PhD[57]; Paul E. Pfeffer MRCP(UK), PhD[58,59]; Celeste M. Porsbjerg, MD, PhD[60], Todor A. Popov, MD, PhD[61]; Chin Kook Rhee, MD, PhD[62]; Sundeep Salvi, MD, PhD[63]; Camille Taillé, MD, PhD[64]; Christian Taube, MD[65]; Carlos A. Torres-Duque, MD[66]; Charlotte S. Ulrik, MD, DMSc, FERS[67]; Seung Won Ra, MD, PhD[68]; Eileen Wang MD, MPH[31,32]; Michael E. Wechsler, MD[69]; David B. Price, FRCGP[4,5,70]

Supplementary Table 1: A summary of how each registry diagnoses asthma and categorizes severe asthma

Country	Severe Asthma Definition*	Diagnosis Confirmation	Age of asthma onset
Argentina **Bulgaria** **Canada** **Greece** **India** **Ireland** **Japan**	ERS/ATS Task Force guidelines on assessment and treatment of severe asthma, based on GINA guidelines for asthma control; a stepwise approach towards pharmacotherapy. 1) GINA Step 5 if: At least one of the following: a) Anti-immunoglobulin E (omalizumab) b) Anti-interleukin-5 (mepolizumab, reslizumab, benralizumab) c) Anti-interleukin-4 (dupilumab) d) Bronchial thermoplasty, e) Maintenance oral corticosteroids.	1) Clinical diagnosis of severe asthma OR 2) Clinical opinion by physicians (according to severe asthma definition)	1) Age at which asthma is first diagnosed OR 2) Age at which asthma symptoms were first observed (Whichever occurred first)

Kuwait
 	
Saudi Arabia
 	
South Korea
 	
Taiwan
 	
United Arab Emirates
	OR
	
	2)
	
	a) GINA Step 4 if:
	
	Medium to High dose ICS plus second controller (LABA AND/OR LAMA)
	
	WITH/WITHOUT Extra controller (e.g. LTRA AND/OR theophylline)
	
	AND
	
	b) Uncontrolled asthma if at least one of the following is fulfilled:
	
	• Poor symptom control:
	  ○ ACQ[1] >1.5, OR
	  ○ ACT[2] <20, OR
	  ○ Having at least 3 of the following during the past 4 weeks (NAEPP/GINA guidelines):
	  • Daytime symptoms >twice/week,
	  • Night waking due to asthma,
	  • Reliever needed >twice/week,
	  • Activity limitation due to asthma
	• Airflow limitation: FEV_1< 80% predicted (in the face of reduced FEV_1/FVC following a withhold of short and long-acting bronchodilators, i.e. Pre-bronchodilator)		

	• Serious exacerbations: at least one hospitalization, ICU stay or mechanical ventilation in the previous year • Frequent severe asthma exacerbations: two or more short courses of systemic corticosteroids (>3 days course each in the previous year)		
Australia	1) Uncontrolled on GINA Step 4 Treatment -ERS/ATS guideline for uncontrolled asthma: a) Poor symptom control: ACQ consistently >1.5, ACT< 20 (or 'not well controlled' by NAEPP/GINA guidelines) AND/OR b) Frequent severe exacerbations: 2 or more bursts of systemic CSs (>3 days each) in the previous year AND/OR c) Serious exacerbations: at least one hospitalization, ICU stay or mechanical ventilation in the previous year AND/OR d) Persistent airflow limitation: FEV_1< 80% predicted (in the face of reduced FEV_1/FVC following a withhold of short and long acting bronchodilators (i.e. PRE-bronchodilator)	Airflow Obstruction: 1) BDR > 200 mL and/or > 12% 2) AHR in response to any standard challenge agent 3) Peak flow variability >12% 4) FEV_1 Variability >12%	1) Age when asthma symptoms began 2) Age at which asthma was first diagnosed 3) Age of first use of asthma treatment
Colombia	1) GINA Step 4 uncontrolled or GINA Step 5 -ERS/ATS guideline for uncontrolled asthma: a) Poor symptom control: ACQ consistently >1.5, ACT < 20 (or 'not well controlled' by NAEPP/GINA guidelines) AND/OR	1) A clinical diagnosis of asthma plus functional confirmation: a) BDR > 200 mL and > 12%, or	1) Age of onset of asthmatic symptoms

	b) Frequent severe exacerbations: 2 or more bursts of systemic CSs (>3 days each) in the previous year AND/OR c) Serious exacerbations: at least one hospitalization, ICU stay or mechanical ventilation in the previous year AND/OR d) Persistent airflow limitation: FEV_1< 80% predicted (in presence of reduced FEV_1/FVC following a withhold of short and long-acting bronchodilators	b) AHR in response to any standard challenge agent. or c) FEV_1 Variability >12% or PEF variability > 20% 2) If functional confirmation was not obtained, a clinical diagnosis of asthma done by a pulmonologist was accepted.	2) Before age of 12 or after age of 12
Denmark **Mexico**	1) GINA Step 5 Treatment 2) Uncontrolled on GINA Step 4 Treatment -ERS/ATS guideline for uncontrolled asthma: a) Poor symptom control: ACQ consistently >1.5, ACT< 20 (or 'not well controlled' by NAEPP/GINA guidelines) AND/OR b) Frequent severe exacerbations: 2 or more bursts of systemic CSs (>3 days each) in the previous year AND/OR c) Serious exacerbations: at least one hospitalization, ICU stay or mechanical ventilation in the previous year AND/OR	NIL	Age at patient's first asthma symptoms

	d) Persistent airflow limitation: FEV_1< 80% predicted (in the face of reduced FEV_1/FVC following a withhold of short and long-acting bronchodilators (i.e. PRE-bronchodilator)		
Italy	1) ERS/ATS Severe Asthma definition: Asthma which requires treatment with guidelines suggested medications for GINA steps 4–5 asthma for the previous year or systemic CS for ≥50% of the previous year to prevent it from becoming "uncontrolled" or which remains "uncontrolled" despite this therapy	1) Method of diagnosis: (a) Methacholine (b) Bronchodilation (c) Functional Respiratory Variability	1) Age of asthma onset 2) Age at diagnosis
Spain	1) GEMA Step 5 or Step 6 Treatment 2) Uncontrolled on GEMA Step 4 Treatment: a) Symptoms of severe asthma b) Frequent exacerbations that require the use of systemic corticosteroids	NIL	Year of asthma diagnosis
UK	1) ERS/ATS Severe Asthma definition: Asthma which requires treatment with guidelines suggested medications for GINA steps 4–5 asthma for the previous year or systemic CS for ≥50% of the previous year to prevent it from becoming "uncontrolled" or which remains "uncontrolled" despite this therapy	NIL	Date first seen by the chest physician

*All patients included in the current study met ISAR's standardized definition of severe asthma

ACQ: Asthma Control Questionnaire; ACT: Asthma Control Test; AHR: airway hyper-responsiveness; ATS: American Thoracic Society; BDR: bronchodilator response; ERS: European Respiratory Society; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; GEMA: Spanish guideline on the management of asthma; GINA: Global Initiative for Asthma; CS: corticosteroid; ICS: inhaled corticosteroid; ICU: intensive care unit; LABA: long-acting β_2-agonist; LAMA: long-acting muscarinic receptor antagonist; LTRA: leukotriene receptor antagonist; NAEPP: National Asthma Education and Prevention Program; PEF: peak expiratory flow rate;

Supplementary Table 2. Baseline demographic variables

Variable Name†	Description
Age Sex Height Weight	Patient age in years, gender, height measurement in metres (m) and weight measurement in kilograms (kg)
Body Mass Index	Defined as the ratio of weight (kg) to squared height (m^2). Categorized as: ● Underweight: < 18.5 kg/m^2, ● Normal weight: ≥ 18.5 kg/m^2 and < 25 kg/m^2, ● Overweight: ≥ 25 kg/m^2 and < 30 kg/m^2 and ● Obese: ≥ 30 kg/m^2
Ethnicity	Caucasian, Asian, African, Mixed, Other, Unknown
Smoking status	Categorised as non-smoker, current smoker, or ex-smoker
Pack years	Defined as the number of cigarettes smoked per day divided by 20 and multiplied by the number of years smoked

†All variables are measured at baseline which is the first patient visit where data are collected for ISAR

Supplementary Table 3. Baseline clinical variables

Variable Name†	Description
ISAR Severe Asthma Criteria	
ISAR inclusion (GINA guidelines)[3]	Patient on GINA Step 5 treatment OR Patient on GINA Step 4 treatment with (a) Severe asthma symptoms (b)Severe asthma exacerbations requiring systemic corticosteroids
Eligibility criteria for biologic therapy	A composite algorithm for biologic initiation eligibility
Medical History	
Asthma duration	Whole years or months (if less than 1 year) at which first asthma diagnosis/symptoms began to the date of entry into the study
Age of asthma onset	Age of first asthma diagnosis/symptoms
Number of exacerbations	Count of exacerbations requiring rescue oral corticosteroids in the past 1 year ● For analysis: continuous and categorical values (1,2,3,4 or more)
Adherence	Yes: Clinical Impression Yes: Prescription Records No
Number of invasive ventilations for severe asthma	Count of episodes of invasive ventilation ever
Number of hospital admissions	Count of hospital admissions for asthma in the past 1 year
Number of emergency department visits	Count of emergency department admissions for asthma in the past 1 year

Asthma control	Categorised as controlled, partly controlled, or uncontrolled according to the GINA Asthma Control Criteria/ACQ[1]/ACT[2], depending on country.
Clinical management plan	Discharge to local service Optimisation of current treatment Biologic therapy Bronchial thermoplasty Maintenance oral corticosteroids Steroid sparing agent Enter into clinical trial Other (please specify) No data
Blood and Sputum Tests	
Immunoglobulin E level	Counts of immunoglobulin E, measured in kilounits per litre (kU/L) or international units per litre (IU/mL) ● Low: < 150 IU/mL ● Moderate: 150-400 IU/mL ● High: >400 IU/mL
Blood eosinophil level	Highest counts of blood eosinophils, measured in cells per microlitre (µL).
Sputum eosinophil level	Highest counts of sputum eosinophils, expressed as percentage (%) of the total cell count.
Allergy Testing	
Skin Prick Test	HDM, animal dander (cat, dog), pollen (tree, grass) and moulds (Aspergillus). ● Categorised as positive reaction if >4 mm is wheal diameter

SPT positive allergens	Grass Mix, Weed Mix, Mould Mix, HDM, Cat, Dog, Trees, Aspergillus, Food Mix, Animal Mix, Aspergillus, Other • Categorised as positive reaction if >0.7 kU/L
Serum Allergen Test	Positive/No/No data
SAT positive allergens	Dust Mite (eg: D. Pteronyssinus), Grass mix, Cat hair, Mould mix, Dog hair, Aspergillus, Other (Please Specify)
Spirometry	
Pre-bronchodilator FEV_1	FEV_1 measured in litres (L), before administering bronchodilator
Pre-Bronchodilator FVC	FVC measured in litres (L) before administering bronchodilator
Post-bronchodilator FEV_1	FEV_1 measured in litres (L), after administering bronchodilator
Post-Bronchodilator FVC	FVC measured in litres (L), after administering bronchodilator
Pre-bronchodilator FEV_1 (percentage of predicted)	Measured pre-bronchodilator FEV_1 as a percentage (%) of predicted FEV_1
Pre-bronchodilator FVC (percentage of predicted)	Measured pre-bronchodilator FVC as a percentage (%) of predicted FVC
Post-bronchodilator FEV_1 (percentage of predicted)	Measured post-bronchodilator FEV_1 as a percentage (%) of predicted FEV_1
Post-Bronchodilator FVC (percentage of predicted)	Measured post-bronchodilator FVC as a percentage (%) of predicted FVC
FEV_1/FVC ratio pre-bronchodilator	
FEV_1/FVC ratio post-bronchodilator	

FeNO test	Measurements of FeNO concentration in exhaled breath, measured in ppb at a flow rate of 50mL/s. Categorized as: ● Low FeNO: <25ppb and ● High FeNO: ≥45 ppb
PC20 Methacholine/Histamine challenge test	Methacholine challenge test (also known as bronchoprovocation test) measured in mg/ml.
Prevalent and New Occurrence of SCS-related Comorbidity‡	
Anxiety/depression	Self reported or diagnosis for Anxiety/depression
Osteoporosis	Self reported or diagnosis for Osteoporosis
Diabetes	Self reported or diagnosis for Diabetes
Peptic ulcer	Self reported or diagnosis for Peptic ulcer
Pneumonia	Self reported or diagnosis for Pneumonia
Serious infection	One or more infections requiring hospitalization, invasive or non-invasive ventilation, IV antibiotics, or resulting in a fatal outcome
Prevalent and New Occurrence of Potentially T2-relatedComorbidity‡	
Allergic rhinitis	Self-reported or diagnosis for Allergic rhinitis
Chronic rhinosinusitis	Self-reported or diagnosis for Chronic rhinosinusitis
Eczema	Self-reported or diagnosis for Eczema
Nasal polyps	Self-reported or diagnosis for Nasal polyps
Obstructive sleep apnea	Self-reported or diagnosis for Obstructive sleep apnea
Renal failure	Self-reported or diagnosis for Renal failure
Overall circulatory diseases	Self-reported or diagnosis for indicated history of Disease of the circulatory system

Heart Failure	Self-reported or diagnosis for Indicated history of heart failure
Myocardial infarction	Self-reported or diagnosis for Myocardial infarction
Thromboembolism	Self-reported or diagnosis for Thromboembolism
Stroke	Self-reported or diagnosis for Stroke
Pulmonary embolism	Self-reported or diagnosis for Pulmonary embolism
Cancer	Self-reported or diagnosis for Cancer
Medication	
Long-term OCS (Y/N, daily dose, duration)	Prescription of OCS for maintenance
ICS+LABA (Y/N, daily dose, duration)	Prescription for ICS+LABA, expected for all
ICS (Y/N, daily dose, duration)	Prescription for ICS
LABA (Y/N, duration)	Prescription for LABA
LAMA (Y/N, duration)	Prescription for LAMA
Theophylline (Y/N, duration)	Prescription for theophylline
LTRA (Y/N, duration)	Prescription for LTRA
Anti-IgE (Y/N, duration)	Prescription for Anti-IgE: Omalizumab
Anti-IL5/IL5R (Y/N, type, duration)	Prescription for Anti-IL5/5R: Mepolizumab, Reslizumab, Benralizumab
Anti-IL4Rα (Y/N, type, duration)	Prescription for Anti-IL4Rα
Macrolide Antibiotic (Y/N, type, duration)	Prescription for Macrolide Antibiotics: Azithromycin, Clarithromycin, Erythromycin, Roxithromycin, Fidaxomicin, Telithromycin,
Other Steroid Sparing Agent	Prescription for Other Steroid Sparing Agent

†All variables are measured at baseline which is the first patient visit where data are collected for ISAR

‡time to collect co-morbidity data is relatively short. Only co-morbidities with substantial data will be analyzed for this study

ACT: Asthma Control Test; ACQ: Asthma Control Questionnaire; FeNO: fractional exhaled nitric oxide; FEV_1; forced expiratory volume in one second; FVC; forced vital capacity; GINA: Global Initiative for Asthma; HDM: house dust mite; ICS: inhaled corticosteroid; IgE: immunoglobulin E; IL-4Rα: interleukin-4 receptor α; IL-5/5R: interleukin-5/5 receptor; ISAR: International Severe Asthma Registry; LABA: long-acting β2-agonist; LAMA: long-acting muscarinic antagonist; LTRA: leukotriene receptor antagonist; PC20: methacholine challenge test; OCS: oral corticosteroid; ppb: parts per billion; SAT: serological allergy test; SCS: systemic corticosteroid; SPT: skin prick test;

Supplementary Table 4. Biologic Accessibility Score (BACS) Index§ by Country

Country	No. of patients who did not initiate biologics in cohort	No. of patients who initiated biologics in cohort	Total patients in cohort	BACS (Anti-IL-5/5R*)	BACS (Anti-IgE**)	BACS (Anti-IL-4Rα***)
Argentina	6	1	7	61	48	NIL
Australia	40	43	83	30	39	48
Bulgaria	6	4	10	29	43	NIL
Canada	7	23	30	49	59	NIL
Colombia	17	1	18	40	55	33
Denmark	3	170	173	56	71	51
Greece	3	10	13	56	64	NIL
India	3	0	3	NIL	NIL	NIL
Ireland	8	0	8	51	NIL	NIL
Italy	101	136	237	63	61	74
Japan	15	6	21	56	59	55
Kuwait	18	70	88	56	64	38
Mexico	7	9	16	74	67	88
Saudi Arabia	12	15	27	56	64	64
South Korea	18	2	20	72	52	64
Spain	3	7	10	58	58	NIL
Taiwan	18	4	22	32	61	NIL
UAE	3	0	3	NIL	NIL	NIL
UK	128	495	623	43	55	NIL

IgE: immunoglobulin E; IL-4Rα: interleukin-4 receptor α; IL-5/5R: interleukin-5/5 receptor; UAE: United Arab Emirates: UK: United Kingdom

§A biologic accessibility score (BACS) has been developed by Porsbjerg and colleagues[4] to determine the ease of receiving a biologic in various countries. The BACS is a composite score incorporating ten prescription access criteria (i.e. age, severe/phenotype, serum IgE, FeNO, allergic asthma, background therapy, OCS, exacerbations, asthma control, and lung function), each with a maximum score of 10 points. The calculated BACS thus reflects a country's ease of access to biologics.

* The BACS Index included here is the average of the BACS Index for mepolizumab, reslizumab, and benralizumab.

** The BACS Index included here is for omalizumab.

*** The BACS Index included here is for dupilumab.

Supplementary Table 5. Range of exacerbation counts (over the past year) by country

Country	No. of observations with exacerbation data	Minimum	25th Percentile	Median	75th Percentile	Maximum	Mean
Argentina	6	1	3	3	3	8	3.5
Australia	15	0	1	4	4	25	4.3
Bulgaria	9	2	2	4	4	8	3.9
Canada	26	0	2	5	5	16	4.9
Colombia	17	0	1	4	5	7	3.5
Denmark	168	0	2	4	6	13	4.1
Greece	13	0	2	5	5	10	4.4
India	3	1	1	4	6	6	3.7
Ireland	8	4	4.5	5.5	10	15	4.1
Italy	229	0	2	3	5	30	4.1
Japan	21	0	3	4	8	31	7.8
Kuwait	88	0	4	5	6	10	5.0
Mexico	16	0	1	3.5	4.5	6	3.1
Saudi Arabia	26	0	4	5	12	30	8.9
South Korea	20	0	0	0	3.5	5	1.4
Spain	10	4	4	4	5	7	4.7
Taiwan	20	0	1.5	4	5.5	11	4.1
UAE	3	5	5	5	12	12	7.3
UK	619	0	3	5	8	24	5.6

UAE: United Arab Emirates; UK: United Kingdom

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