Biologic Utilisation Patterns: Data From The International Severe Asthma Registry (ISAR)

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Introduction

Rationale

- There is a paucity of literature on both the frequency and patterns of biologic use after biologic prescription taking into account documented inter-country differences in health care system and biologic availability.[1-3]

Objective

- To describe the frequency of biologic treatment and patterns of biologic use in a global real-life severe asthma cohort.

Methods

Data source

- Historical cohort study using data extracted from the International Severe Asthma Registry (ISAR) on 1 Sept 2019.
  - ISAR is a multinational, observational epidemiologic data repository, containing data on patients with severe asthma aged ≥18 years on GINA 2018 Treatment Step 5 or with uncontrolled asthma on GINA Step 4.

Patients

- Enrolled from 11 ISAR countries and providing data from January 2015 to September 2019 **(Table 1)**.
- Treated with anti-IgE (omalizumab), anti–IL-4R (dupilumab) or anti–IL-5/5R (mepolizumab, reslizumab, benralizumab).

Country-specific biologic questionnaire

- Information on country-specific biologic licensing, reimbursement, prescribing and stopping rules/guidelines was collected from these 11 countries using a semi-structured online questionnaire.
  - Time for safety or efficacy was defined as the length of time a country used to determine if a patient was responding adequately to a biologic.

Analyses

- Patient biologic utilization patterns were described for the total population and for each country (stratified by length of time when ≥2 biologics were available) as:
  - **Continued**: patients on a single biologic from date of biologic initiation, to point of data extraction (1 Sep 2019), with ≥6 months of follow-up data, which indicated that the patient had neither stopped nor switched their initiation biologic.
  - **Switched**: patients who used ≥1 biologic during follow-up, with no restriction on time between biologics.
  - **Stopped**: patients who stopped their first and only biologic, with no time criterion.
- Switch patterns were also investigated for all patients who switched biologic at least once and for those who switched multiple times.

Results

Country specific biologic questionnaire (Table 1)

- All countries had ≥2 biologics available at the time of data extraction (September 2019).
- Omalizumab and mepolizumab were available in all 11 countries.
- Benralizumab (81.2%), reslizumab (63.6%), and dupilumab (54.5%) were available in most countries.
- Overall, the majority (8/11) of countries reported time of efficacy assessment being at 4–12 months.

Table 1: Number and classes of biologics available in 11 ISAR countries studied

Number of Biologics	Biologic	Country
5	omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab	USA, DK
4	omalizumab, mepolizumab, benralizumab, dupilumab	JP, KW, IT, ESP, CAN
4	omalizumab, mepolizumab, reslizumab, benralizumab	UK
3	omalizumab, mepolizumab, benralizumab,	BG
3	omalizumab, mepolizumab, reslizumab	SK
2	omalizumab, mepolizumab	GR

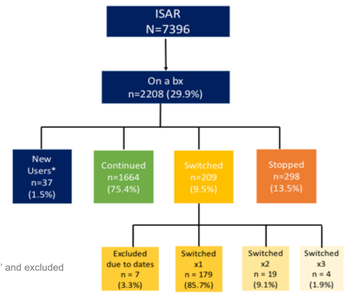
Legend: Ig: Immunoglobulin; IL: interleukin; ISAR: international Severe Asthma Registry; BG: Bulgaria; CAN: Canada; DK: Denmark; ESP: Spain; GR: Greece; IT: Italy; JP: Japan; KW: Kuwait; SK: South Korea; UK: United Kingdom; USA: United States of America *as of 30th Sept 2019

Results

Patterns of biologic use: total population

- A total of 2208 patients with severe asthma managed in specialist asthma centers from around the world were included.
- Of these patients, the majority (75.4%) continued their biologic.
- A small proportion of patients stopped (13.5%) or switched (9.5%) biologic during the course of follow-up (**Figure 1**).

Figure 1: Patient flow diagram of pattern of biologic use



Legend: Bx: biologic; ISAR: International Severe Asthma Registry
7 out of 209 switchers did not have sufficient data to inform order of biologic switch
*insufficient follow-up time to ascribe a pattern of use and were deemed 'new users' and excluded from subsequent analysis.

Patterns of biologic use: individual countries

- Japan and the USA had the highest proportion of stopped users, whereas SK had the highest proportion of biologic switchers, although absolute numbers were low (**Table 2**).
- Countries could be categorized according to ratio of switchers to stoppers
  - Higher proportion of stoppers to switchers: USA, UK, & ES
  - Higher proportion of switchers to stoppers: KW, BG, CN, DK, SK, GR
  - Equal proportion of stoppers & switchers: JN & IT

Table 2: Country-specific biologic utilization groups, stratified by length of time with ≥2 biologics

Time with ≥2 biologics available	Country	Continued	Switched	Stopped
N (%)	ISAR (n=2171)	1664 (76.7)	209 (9.6)	298 (13.7)
2 years	Japan(n=17)	11 (64.7)	3 (17.7)	3 (17.7)
3 years	Kuwait (n=143)	123 (86.0)	18 (12.6)	2 (1.4)
4 years	Bulgaria (n=30)	27 (90.0)	2 (6.7)	1 (3.3)
	Canada (n=58)	47 (81.0)	8 (13.0)	3 (5.2)
	Denmark (n=132)	112 (84.9)	20 (15.2)	0 (0.0)
	(4 year strata Total)	186 (84.6)	30 (13.6)	4 (1.8)
	4 year strata Average	62 (84.5)	10 (13.6)	1.33 (1.8)
5 years	USA (n=914)	575 (62.9)	112 (12.3)	227 (24.8)
	UK (n=263)	236 (86.4)	5 (2.5)	22 (11.1)
	S. Korea (n=5)	3 (60.0)	2 (40.0)	0 (0.0)
	Greece (n=10)	9 (90.0)	1 (10.0)	0 (0.0)
	Italy (n=360)	349 (96.9)	6 (1.7)	5 (1.4)
	Spain (n=199)	172 (86.4)	5 (2.5)	22 (11.1)
	5 year strata Total	1341(75.1)	156 (8.7)	289 (16.2)
	5 year strata Average	223.5 (75.1)	26 (8.7)	48.2 (16.2)

Switch patterns

- Overall 209 patients switched biologic; of those 202 had sufficient data (**Figure 2**).
  - 179/202 (88.6%) switched biologic only once and 23/202 (11.4%) switched more than once.
- Of the first biologic switches, the most common patterns were going from omalizumab to mepolizumab (n=101), followed by going from mepolizumab to benralizumab (n=35).
- Of patients who switched more than once (n=23), most switched twice (n=20/23; 87.0%) (**Figure 3**).
  - The most common multi-switch was from omalizumab to mepolizumab to benralizumab (n=8/23; 34.8%).

Figure 2: Distribution of first biologic switches among all patients who switched (n=202)

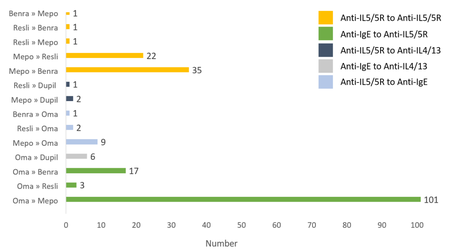
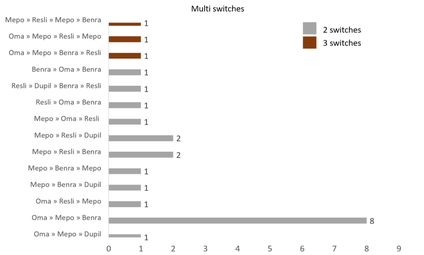


Figure 3: Distribution of second and third switches among individuals switching more than once (n=23)



Conclusions

- **Although the majority of severe asthma patients managed around the world continue with their first prescribed biologic therapy, a minority either stop (13.5%) or switch (9.5%) therapy.**
- **Of those that change biologic, most switch from anti-IgE to an anti–IL-5/5R biologic.**
- **Intercountry variation exists in biologic usage pattern.**
- **More research is needed to discover and better understand the influence of country-specific factors (e.g. reimbursement, availability, guidelines) on our findings.**

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