Characterization of Eosinophilic and Non-Eosinophilic Severe Asthma Phenotypes and Proportion of Patients with these Phenotypes in the International Severe Asthma Registry (ISAR)

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Introduction

- There is increasing recognition of marked phenotypic heterogeneity within severe asthma and of the need to better characterize eosinophilic (EOS) and non-EOS phenotypes.[1]
- Various phenotypic classifications have been suggested, but the data upon which they are based and clinical applicability in the real world are limited.

Aims

- To describe an algorithm to characterize EOS and non-EOS severe asthma phenotypes.
- To quantify the prevalence of these phenotypes in a large international cohort of patients with severe asthma.

Methods

Design

- A cohort study including patients enrolled into the International Severe Asthma Registry (ISAR) between 1 Jan 2015 and 30 Sept 2019.

Patients

- Aged ≥18 years, with severe asthma (i.e. receiving treatment at GINA Step 5 or with uncontrolled asthma at GINA Step 4)[3] and ≥1 recorded blood eosinophil count (BEC).
  - Pre-biologic BEC was used for patients on anti–interleukin 5 (IL-5) or anti–interleukin 5-receptor α (IL-5R) therapy.

Data

- Prospective, de-identified, standardized patient data collected from new and pre-existing severe asthma registries contributing to ISAR from 11 countries.

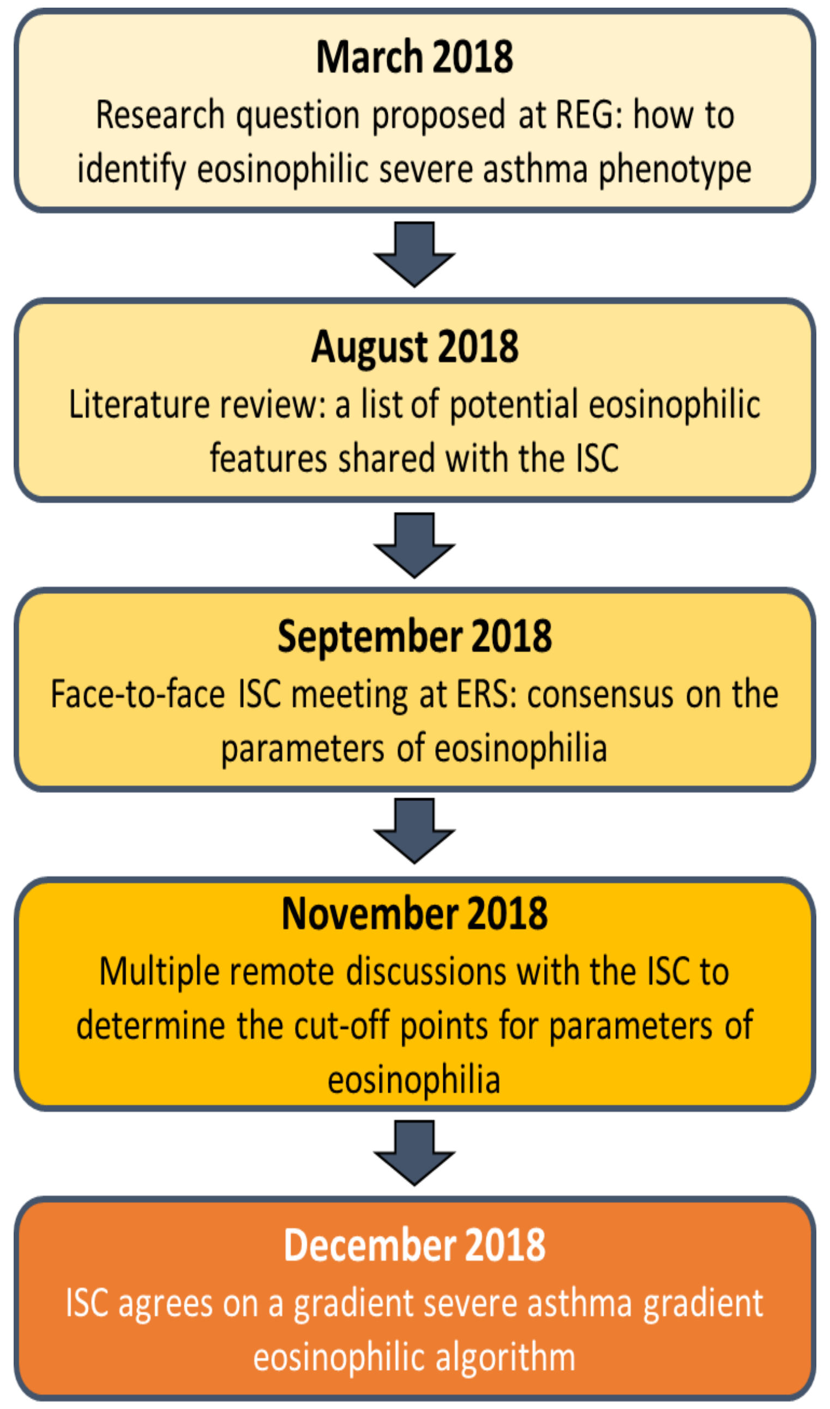
Development of a gradient eosinophilic algorithm

- Developed following an extensive literature review and consensus with experts of the ISAR Steering Committee (**Figure 1**).
- Variables used to inform the algorithm were selected and cut-off values agreed. These included highest BEC ever or pre-anti–IL-5 (≥300, ≥150-300, <150 cells/µL), long-term oral corticosteroid (OCS), elevated fractional exhaled nitric oxide (FeNO ≥25 ppb) ever, indication of nasal polyps ever, and adult onset of asthma (age ≥18 years).

Analysis

- Phenotypes were classified as Grade 0 (non-EOS), Grade 1 (least likely EOS), Grade 2 (likely EOS) and Grade 3 (most-likely EOS) and the number (%) of patients within each of these EOS classifications calculated.

Figure 1: Process flow chart for development of gradient eosinophilic severe asthma algorithm



March 2018
Research question proposed at REG: how to identify eosinophilic severe asthma phenotype

August 2018
Literature review: a list of potential eosinophilic features shared with the ISC

September 2018
Face-to-face ISC meeting at ERS: consensus on the parameters of eosinophilia

November 2018
Multiple remote discussions with the ISC to determine the cut-off points for parameters of eosinophilia

December 2018
ISC agrees on a gradient severe asthma gradient eosinophilic algorithm

REG: Respiratory Effectiveness Group
ISC: International Severe Asthma Registry Steering Committee
ERS: European Respiratory Society

Results

Patients

- Prospective, de-identified, standardized data were available for 1716 patients (USA: n=70; UK: n=712; ES: n=217; IT: n=163; KW: n=158; DK: n=127: BU: n=87; CA: n=85; GR: n=35; JP: n=34; KR: n=28).

Gradient eosinophilic phenotype algorithm

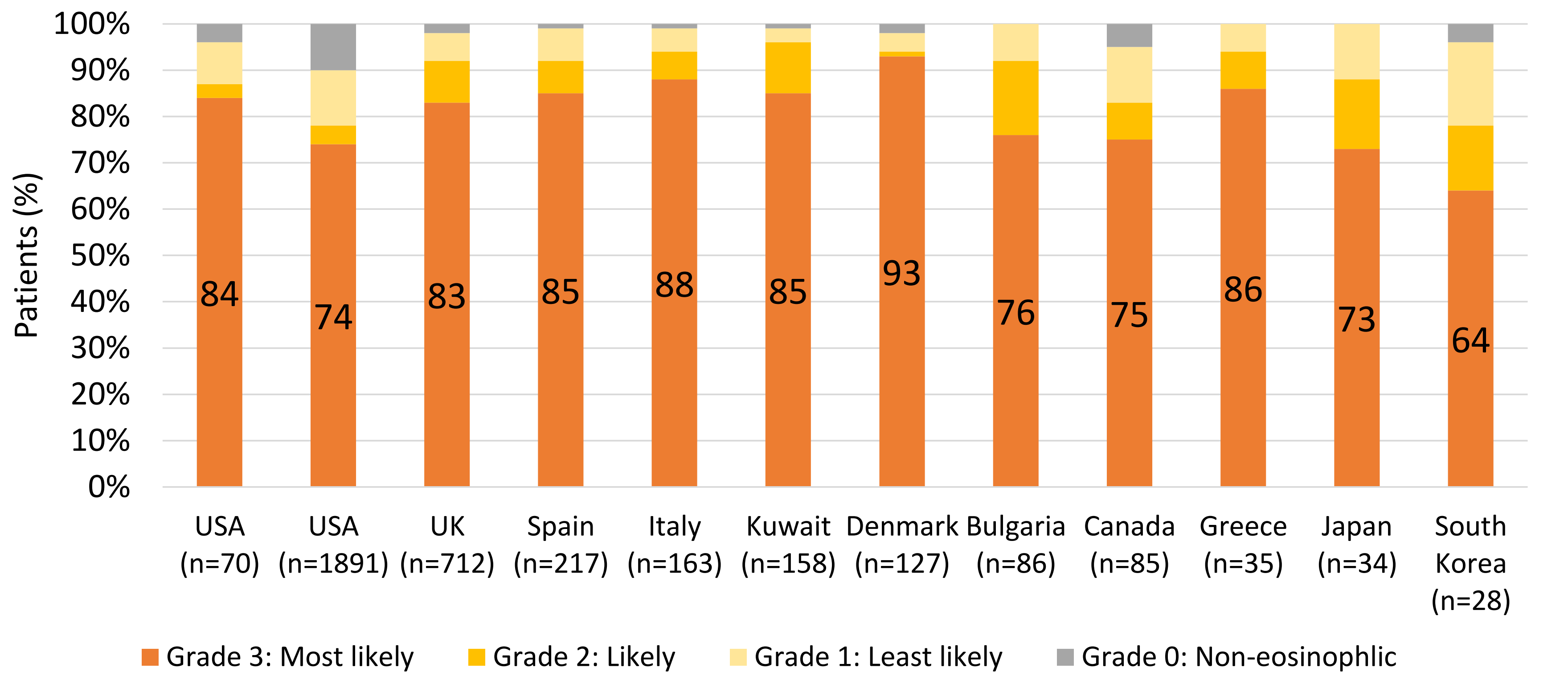
- The most-likely EOS patients (Grade 3) were defined as those with (**Table 1**):
  - Highest BEC ever ≥300 cells/µL, OR on anti–IL-5/5R therapy, OR
  - Highest BEC ever ≥150 to <300 cells/µL AND on long-term OCS, OR
  - Highest BEC ever ≥150 to 300 cells/µL NOT on long-term OCS, BUT with ≥2 of the following: nasal polyps ever, high FeNO, or adult onset.
- Definitions of Grade 0, Grade 1 and Grade 2 are shown in **Table 1**.
- Overall, 83.8% of patients (n=1438) most likely had an EOS phenotype (**Table 1**)
  - 8.3% (n=142), 6.3% (n=108) and 1.6% (n=28) of patients were characterized as 'likely', 'unlikely', and 'non-eosinophilic', respectively.
- Grade 3 (most-likely) EOS phenotype predominated for patients with severe asthma in all countries, ranging from 64% of patients from South Korea to 93% of patients from Denmark (**Figure 2**).

Table 1: Characterization of EOS and non-EOS phenotypes and the proportion of patients with severe asthma with these phenotypes in ISAR (N=1716)

Highest BEC available (cells/µL)[a]	Treatment or clinical characteristic	Eosinophilic phenotype	Prospective ISAR population (n=1716)	
			Number of patients	% patients
≥300		Grade 3: most likely	1196	83.8%
	Anti–IL-5/5R	Grade 3: most likely	178*	
≥150 to < 300	Long-term OCS	Grade 3: most likely	37	
	Presence of ≥2 of the following: NP, FeNO ≥25 ppb, or adult onset[b] (no long-term OCS)	Grade 3: most likely	27	
	Either nasal polyps, FeNO ≥25 ppb, or adult onset (no long-term OCS)	Grade 2: likely	67	3.9%
	No nasal polyps, elevated FeNO, adult onset, or long-term OCS	Grade 1: least likely	27	1.6%
<150	Long term OCS	Grade 2: likely	75	4.4%
	Either nasal polyps, FeNO ≥25 ppb, or adult onset (no long-term OCS)	Grade 1: least likely	81	4.7%
	No nasal polyps, elevated FeNO, adult onset, or long-term OCS	Grade 0: unlikely (non-eosinophilic)	28	1.6%

BEC: blood eosinophil count; FeNO: fractional exhaled nitric oxide; IL-5: interleukin 5; IL-5R: interleukin 5-receptor α; ISAR: International Severe Asthma Registry; OCS: oral corticosteroids. [a]independent criteria specified in each row; [b]aged ≥18 years at onset of asthma
Pre–anti–IL-5/5R or maintenance OCS was used wherever possible; *of these patients n=53 had a BEC ≤ 150 to <300 and n=125 had a BEC <150 of which n=37 had never had mOCS. However n=26 of these 37 patients did not have a pre-anti-IL-5 BEC.

Figure 2: Eosinophilic severe asthma phenotype distribution by country for prospective ISAR population



Conclusion

- **We have developed a clinical algorithm to improve the identification of EOS and non-EOS phenotypes in a real-world severe asthma population.**
- **The majority of patients seen across severe asthma centers globally have eosinophilic disease.**
- **We recommend the implementation of this gradient algorithm in a different severe asthma study population with longitudinal BEC records to assess the specificity of EOS phenotype definition and to assess the generalizability of the reported results to the broader asthma population.**

References

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Conflict of interest statement: