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BIOLOGICAL TREATMENTS IN ALLERGY: PRESCRIBING PATTERNS AND MANAGEMENT OF HYPERSENSITIVITY REACTIONS

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CONFLICT OF INTERESTS:

The authors declare that they do not have conflict of interests related to the contents of this article.

Clinical implications : Biological agents (BA) are becoming essential treatments in allergy, but are not available worldwide. Allergists are not authorised to prescribe them in all countries. BA are generally safe, but severe hypersensitivity reactions can occur requiring guided allergological workup and management.

Biological therapies (BA) are emerging as potential effective treatment for allergic and hypersensitivity disorders (A/H). Four main classes of BA are now (May 2020) approved by US Food and Drug Administration and European Medicines Agency for A/H: Anti-immunoglobulin E (IgE) (Omalizumab) (1), Anti-interleukin 5 (IL5) (Mepolizumab, Reslizumab) (2), Anti-IL4/13 (Dupilumab) (3) and Anti-IL5 R (Benralizumab) (4). Hypersensitivity reactions (HSR) due to BA can occur with different severity degrees, which hamper their use. New types of HSR have been reported with lack of standardized and guided allergy work-up.

Given the novelty of these therapeutics and new challenges faced by the allergy community, we proposed an international survey, which sought to evaluate different aspects related to BA used in the management of HSR due to these drugs.

A web-based survey was undertaken to reach out the worldwide allergy community by e-mail and social media. The web-questionnaire, in English and in French, was constructed using GoogleDocs® and contained 18 questions covering demographic data from participants, BA prescription and related expenses, frequency of HSR and how they are managed (Online Repository Text). It was circulated for 5 weeks and had anonymous and volunteer standards. We received the support from the French Allergy Syndicate (FAS) to send it to their members.

Data are presented for 348 participants from 59 countries of all continents. The countries were aggregated according to world regions: North America (NA), Latin America (LA), Europe (EU), Africa and Middle East (AFR/ME), Asia Pacific (AP). Most of the respondents were from EU (62.6%), 87% were allergists with long-term professional experience, 61% worked in a public institution (Table 1).

BA were prescribed by 78.4% of respondents, once or less than once per week (54.6%). Right to prescribe BA was restricted to 68% of allergists. Almost all allergists in EU did not have the right to issue first prescription BA (96.5%), remarkably in France (91%). The most commonly prescribed BA worldwide was the anti-IgE (78%), followed by anti-IL5 (43.9%) then anti-IL13R-IL4R (36.7%) and anti-IL5R (26.7%). NA recorded a higher rate of prescription of new BA (Table 1). The trends of prescription may follow the dynamic of the commercial availability of the BA in the market.

Expenses for BA were mostly completely covered by national social security (59.7%), depending of the country jurisdiction. They were covered by the patient in 10% of cases and by private insurance for 9.1% of respondents. Cost of BA remains an issue from the public health perspective, it is estimated at $10,000 to $30,000 per year/patient receiving BA. Biosimilars drugs, or highly similar copies of BA, will help reducing costs, but while EU has at least 40 biosimilars approved in 2018, US only has five commercially available (5).

The most reported HSR were local reactions at the site of the injection (74%) followed by anaphylaxis (6.8%) and delayed exanthemas (5.1%). Severe cutaneous adverse reactions were rarely reported (<1%). Although these reactions can be allergic (immediate or delayed), most are irritative and can be managed with symptomatic treatment and tends to decrease in frequency and severity with continuation of the injections.

Respondents relied on published data to manage HSR (45.4%), manly national (34.1%) and local recommendations (10%). Lack of national or regional formal recommendations have been reported in 13.5% of respondents.

For mild HSR, most continued ("treated through") the BA, treated the reaction symptomatically (54.6%) and rarely performed allergy investigations (20.7%). For moderate to severe reactions, most decided for switching for an alternative BA (40.5%), but 31% stopped the BA and switched to a non-biological treatment. Allergy work-up was carried out by 28% of respondents. Desensitization was considered in 18.9% of cases (Table 2). Existing literature estimates the risk of developing anaphylaxis due to omalizumab by 0.09% and by 0.3% to Reslizumab, most (77%) during the first 2 hours after the administration. The pathophysiology of anaphylaxis remains unclear and it seems that there is no apparent correlation between the severity of anaphylaxis and skin test reactivity or the presence of IgE antibodies. Different anaphylaxis phenotypes and endotypes have been identified (6). However, the treatment of the acute reaction remains the same recommended to anaphylaxis.

Allergy tests were infrequently performed by the participants, but should be encouraged to define the mechanism and drug causality of the HSR. Desensitization should be recommended to proven IgE reactions but the decision should be taken individually. For other reactions, desensitization or drug challenge can be considered depending on the severity of the reactions, and the need for the BA (7-9).

Delayed reactions were the less frequent type of HSR in our survey, mainly represented by serum sickness like-reaction causing local or systemic injury. Serum sickness like-reaction have been reported 1 to 5 days after the infusion of omalizumab, presenting fever, arthralgia/arthritis, jaw pain or tightness, erythematous skin eruption, purpura and conjunctival hyperemia. Although serum sickness

reactions are typically self-limited, re-administration of the culprit BA should not be considered. Other types of delayed HSR to BA remain rare and limited to case reports.

Our study presents some limitations. The initial sample size was not assessed due to the methodology of dissemination. Although we had a limited number and regional/geographical heterogeneity of responses, the qualitative analysis was prioritized. We had higher proportion of responses from France due to the collaboration with the French allergists' community.

This first worldwide survey assessing real-life data from the allergy community provided a snapshot of patterns of prescription of BA used in A/H and information regarding the management of HSR to BA. Although BA are useful in the management of A/H, its prescription seems to be heterogeneous from the international perspective. In several countries, the prescription of BA is restricted to certain authorized specialties, such as dermatologists, pediatricians and pneumologists. The prescription rights of BA may be related to the recognition of allergy as a full specialty nationally and the region/country specialty developments. For instance, in France, allergy has been recognized as a full specialty only in 2017 and the rights to prescribe BA may follow this process, but it is still not a reality as demonstrated in our survey. Most of HSR due to BA are mild local reactions, but severe HSR can occur requiring guided allergy workup and management. There is a lack of consensus of how to manage these HSR, which led us to suggest a decision tree flowchart (Figure E1), which should be validated in the near future.

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CONTRIBUTIONS:

The first and last authors contributed to the construction of the document (designed the study, designed the questionnaire, analysed and interpreted the data, and wrote the manuscript). All the authors critically revised and approved the final version of the manuscript and agree to be accountable for all the aspects of the work.

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LIST OF TABLES

Table 1. Demographic data of respondents and prescription of biological agents (*AME Africa/Middle-East, AP Asia-Pacific, EU Europe, LA Latin America, NA North America)*.

Characteristics	***NA %*** ***(n/total)***	***LA %*** ***(n/total)***	***EU %*** ***(n/total)***	***AME %*** ***(n/total)***	***AP %*** ***(n/total)***	***Total %*** ***(n)***
Number of responses	**22**	**75**	**218**	**16**	**17**	**348**
N (%)	**(6.3)**	**(21.5)**	**(62.6)**	**(4.6)**	**(4.9)**	**(100)**
Specialty[1]						
Allergy	100% (22/22)	92% (69/75)	85.7% (187/218)	87.5% (14/16)	76.4% (13/17)	87.6% (305)
Clinical immunology	54.5% (12/22)	32% (24/75)	13.7% (30/218)	56.2% (9/16)	11.7% (2/17)	22.1% (77)
Dermatology	0% (0/22)	0% (0/75)	6.8% (15/218)	0% (0/16)	11.7% (2/17)	4.8% (17)
Internal Medicine	27.2% (6/22)	6.6% (5/75)	5.9% (13/218)	31.2% (5/16)	5.8% (1/17)	8.6% (30)
General Medicine	0% (0/22)	1.3% (1/75)	8.2% (18/218)	0% (0/16)	0% (0/17)	5.4% (19)
Paediatrics	9% (2/22)	13.3% (10/75)	11.9% (26/218)	12.5% (2/16)	35.3% (6/17)	13.2% (46)
Pneumology	0% (0/22)	4% (3/75)	11% (24/218)	12.5% (2/16)	5.8% (1/17)	8.6% (30)
Gender						
Female	41% (9/22)	38.6% (29/75)	63.7% (139/218)	50% (8/16)	29.4% (5/17)	54.5% (190)
Male	59% (13/22)	61.3% (46/75)	36.2% (79/218)	50% (8/16)	70.5% (12/17)	45.4% (158)
Age						
≤ 40 years	31.8% (7/22)	17.3% (13/75)	40.3% (88/218)	18.7% (3/16)	41.1% (7/17)	33.9% (118)
> 40 years	68.1 % (15/22)	82.6% (62/75)	59.6% (130/218)	81.2% (13/16)	58.8% (10/17)	66% (230)
Place of work[1]						
Public hospital	45.4% (10/22)	40% (30/75)	71.5% (156/218)	43.7% (7/16)	64.7% (11/17)	61.4% (214)
Private hospital	36.3% (8/22)	38.6% (29/75)	12.3% (27/218)	37.5% (6/16)	5.8% (1/17)	20.4% (71)

Private office	13.6% (3/22)	73.3% (55/75)	33.4% (73/218)	37.5% (6/16)	11.7% (2/17)	39.9% (139)
Recognition of Allergy as						
Full specialty	63.6% (14/22)	61.3% (46/75)	80.7% (176/218)	18.7% (3/16)	17.6% (3/17)	69.5% (242/348)
Subspecialty	36.3% (8/22)	34.6% (26/75)	13.7% (30/218)	75% (12/16)	52.9% (9/17)	24.4% (85/348)
Post graduate topic	0% (0/22)	2.6% (2/75)	4.5% (10/218)	6.2% (1/16)	23.5% (4/17)	4.8% (17/348)
Type of Biological Agent prescribed[1]						
Anti IgE (omalizumab)	100% (22/22)	85.3% (64/75)	72% (157/218)	87.5% (14/16)	88.3% (15/17)	78.1% (272/348)
Anti IL5 (Mepolizumab, Reslizumab)	95.4% (21/22)	30.6% (23/75)	45.8% (100/218)	37.5% (6/16)	17.6% (3/17)	43.9% (153/348)
Anti IL5R (Benralizumab)	72.7% (16/22)	12% (9/75)	29.3% (64/218)	18.7% (3/16)	5.8% (1/17)	26.7% (93/348)
Anti IL13R-IL4R (dupilumab)	90.9% (20/22)	45.3% (34/75)	29.3% (64/218)	43.7% (7/16)	17.6% (3/17)	36.7% (128/348)
IL-1 antagonists (anakinra, canakinumab, rilonacept)	18.1% (4/22)	8% (6/75)	8.7% (19/218)	12.5% (2/16)	11.7% (2/17)	9.4% (33/348)
TNF alpha antagonists (infliximab, Etanercept, Adalimumab…)	9% (2/22)	14.6% (11/75)	7.3% (16/218)	31.2% (5/16)	17.6% (3/17)	11.2% (39/348)
Anti CD20 (Rituximab…)	22.7% (5/22)	13.3% (10/75)	6.8% (15/218)	31.2% (5/16)	11.7% (2/17)	10.9% (38/348)
Right of prescription of BA by allergists						
Yes	100% (22/22)	97.3% (73/75)	56.8% (124/218)	100% (16/16)	88.2% (15/17)	71.8% (250/348)
No	0% (0/22)	2.6% (2/75)	38.9% (85/218)	0% (0/16)	5.8% (1/17)	25.2% (88/348)
Prescription of BA in clinical practice						
Yes	100% (22/22)	88% (66/75)	72%	93.7%	76.4%	78.4%

			(157/218)	(15/16)	(13/17)	(273/348)
No	0% (0/22)	12% (9/75)	27% (59/218)	6.2% (1/16)	23.5% (4/17)	20.9% (73/348)

[1]*respondents could choose more than one option*

Table 2. Management of hypersensitivity reactions due to biological agents depending on the severity of the reaction (BA = biological agents, HSR: hypersensitivity reaction)

	Mild to moderate HSR % **(n/total)**	**Severe HSR %** **(n/total)**
	Actions	
Pursue the same BA and treat the reaction symptomatically	53.7% (187/348)	3.7% (13/348)
Switch of the BA	16.6% (58/348)	40.5% (141/348)
Stop the BA and carry on with non-biological treatment	8.6% (30/348)	31.3% (109/348)
Allergic investigation (in vivo/in vitro tests)	21.5% (75/348)	27.5% (96/348)
Desensitization	12.3% (43/348)	18.9% (66/348)