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# 1 BIOLOGICAL TREATMENTS IN ALLERGY: PRESCRIBING PATTERNS AND 2 MANAGEMENT OF HYPERSENSITIVITY REACTIONS

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50 **KEYWORDS:** "Allergy and Immunology", "allergists", "asthma", "atopic eczema", "biological therapy",  
51 "hypersensitivity", "allergic reaction", "Drug-Related side effects and adverse reactions »

## 52 **CONFLICT OF INTERESTS:**

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

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

58

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

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

69 A web-based survey was undertaken to reach out the worldwide allergy community by e-mail and  
70 social media. The web-questionnaire, in English and in French, was constructed using GoogleDocs®  
71 and contained 18 questions covering demographic data from participants, BA prescription and related  
72 expenses, frequency of HSR and how they are managed (Online Repository Text). It was circulated for  
73 5 weeks and had anonymous and volunteer standards. We received the support from the French  
74 Allergy Syndicate (FAS) to send it to their members.

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

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

85 Expenses for BA were mostly completely covered by national social security (59.7%), depending of the  
86 country jurisdiction. They were covered by the patient in 10% of cases and by private insurance for  
87 9.1% of respondents. Cost of BA remains an issue from the public health perspective, it is estimated  
88 at \$10,000 to \$30,000 per year/patient receiving BA. Biosimilars drugs, or highly similar copies of BA,  
89 will help reducing costs, but while EU has at least 40 biosimilars approved in 2018, US only has five  
90 commercially available (5).

91 The most reported HSR were local reactions at the site of the injection (74%) followed by anaphylaxis  
92 (6.8%) and delayed exanthemas (5.1%). Severe cutaneous adverse reactions were rarely reported  
93 (<1%). Although these reactions can be allergic (immediate or delayed), most are irritative and can be  
94 managed with symptomatic treatment and tends to decrease in frequency and severity with  
95 continuation of the injections.

96 Respondents relied on published data to manage HSR (45.4%), mainly national (34.1%) and local  
97 recommendations (10%). Lack of national or regional formal recommendations have been reported in  
98 13.5% of respondents.

99 For mild HSR, most continued (“treated through”) the BA, treated the reaction symptomatically  
100 (54.6%) and rarely performed allergy investigations (20.7%). For moderate to severe reactions, most  
101 decided for switching for an alternative BA (40.5%), but 31% stopped the BA and switched to a non-  
102 biological treatment. Allergy work-up was carried out by 28% of respondents. Desensitization was  
103 considered in 18.9% of cases (Table 2). Existing literature estimates the risk of developing anaphylaxis  
104 due to omalizumab by 0.09% and by 0.3% to Reslizumab, most (77%) during the first 2 hours after the  
105 administration. The pathophysiology of anaphylaxis remains unclear and it seems that there is no  
106 apparent correlation between the severity of anaphylaxis and skin test reactivity or the presence of  
107 IgE antibodies. Different anaphylaxis phenotypes and endotypes have been identified (6). However,  
108 the treatment of the acute reaction remains the same recommended to anaphylaxis.

109 Allergy tests were infrequently performed by the participants, but should be encouraged to define the  
110 mechanism and drug causality of the HSR. Desensitization should be recommended to proven IgE  
111 reactions but the decision should be taken individually. For other reactions, desensitization or drug  
112 challenge can be considered depending on the severity of the reactions, and the need for the BA (7-  
113 9).

114 Delayed reactions were the less frequent type of HSR in our survey, mainly represented by serum  
115 sickness like-reaction causing local or systemic injury. Serum sickness like-reaction have been reported  
116 1 to 5 days after the infusion of omalizumab, presenting fever, arthralgia/arthritis, jaw pain or  
117 tightness, erythematous skin eruption, purpura and conjunctival hyperemia. Although serum sickness

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

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

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

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

164

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167 members.

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#### 171 **LIST OF TABLES**

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

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

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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).

<b>Characteristics</b>	<b>NA % (n/total)</b>	<b>LA % (n/total)</b>	<b>EU % (n/total)</b>	<b>AME % (n/total)</b>	<b>AP % (n/total)</b>	<b>Total % (n)</b>
<b>Number of responses</b>	<b>22</b>	<b>75</b>	<b>218</b>	<b>16</b>	<b>17</b>	<b>348</b>
<b>N (%)</b>	<b>(6.3)</b>	<b>(21.5)</b>	<b>(62.6)</b>	<b>(4.6)</b>	<b>(4.9)</b>	<b>(100)</b>
<b>Specialty<sup>1</sup></b>						
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)
<b>Gender</b>						
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)
<b>Age</b>						
≤ 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)
<b>Place of work<sup>1</sup></b>						
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)

	<i>Private office</i>	13.6% (3/22)	73.3% (55/75)	33.4% (73/218)	37.5% (6/16)	11.7% (2/17)	39.9% (139)
<b>Recognition of Allergy as</b>							
	<i>Full specialty</i>	63.6% (14/22)	61.3% (46/75)	80.7% (176/218)	18.7% (3/16)	17.6% (3/17)	69.5% (242/348)
	<i>Subspecialty</i>	36.3% (8/22)	34.6% (26/75)	13.7% (30/218)	75% (12/16)	52.9% (9/17)	24.4% (85/348)
	<i>Post graduate topic</i>	0% (0/22)	2.6% (2/75)	4.5% (10/218)	6.2% (1/16)	23.5% (4/17)	4.8% (17/348)
<b>Type of Biological Agent prescribed<sup>1</sup></b>							
	<i>Anti IgE (omalizumab)</i>	100% (22/22)	85.3% (64/75)	72% (157/218)	87.5% (14/16)	88.3% (15/17)	78.1% (272/348)
	<i>Anti IL5 (Mepolizumab, Reslizumab)</i>	95.4% (21/22)	30.6% (23/75)	45.8% (100/218)	37.5% (6/16)	17.6% (3/17)	43.9% (153/348)
	<i>Anti IL5R (Benralizumab)</i>	72.7% (16/22)	12% (9/75)	29.3% (64/218)	18.7% (3/16)	5.8% (1/17)	26.7% (93/348)
	<i>Anti IL13R-IL4R (dupilumab)</i>	90.9% (20/22)	45.3% (34/75)	29.3% (64/218)	43.7% (7/16)	17.6% (3/17)	36.7% (128/348)
	<i>IL-1 antagonists (anakinra, canakinumab, riloncept)</i>	18.1% (4/22)	8% (6/75)	8.7% (19/218)	12.5% (2/16)	11.7% (2/17)	9.4% (33/348)
	<i>TNF alpha antagonists (infliximab, Etanercept, Adalimumab...)</i>	9% (2/22)	14.6% (11/75)	7.3% (16/218)	31.2% (5/16)	17.6% (3/17)	11.2% (39/348)
	<i>Anti CD20 (Rituximab...)</i>	22.7% (5/22)	13.3% (10/75)	6.8% (15/218)	31.2% (5/16)	11.7% (2/17)	10.9% (38/348)
<b>Right of prescription of BA by allergists</b>							
	<i>Yes</i>	100% (22/22)	97.3% (73/75)	56.8% (124/218)	100% (16/16)	88.2% (15/17)	71.8% (250/348)
	<i>No</i>	0% (0/22)	2.6% (2/75)	38.9% (85/218)	0% (0/16)	5.8% (1/17)	25.2% (88/348)
<b>Prescription of BA in clinical practice</b>							
	<i>Yes</i>	100% (22/22)	88% (66/75)	72% (157/218)	93.7% (15/16)	76.4% (13/17)	78.4% (272/348)



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

<sup>1</sup>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)
<b>Actions</b>		
<i>Pursue the same BA and treat the reaction symptomatically</i>	53.7% (187/348)	3.7% (13/348)
<i>Switch of the BA</i>	16.6% (58/348)	40.5% (141/348)
<i>Stop the BA and carry on with non-biological treatment</i>	8.6% (30/348)	31.3% (109/348)
<b>Allergic investigation (in vivo/in vitro tests)</b>	21.5% (75/348)	27.5% (96/348)
<b>Desensitization</b>	12.3% (43/348)	18.9% (66/348)