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

3 Leyla Barakat¹MD, Maria Jose Torres² MD PhD, Elizabeth J. Phillips^{3,4,5}MD PhD, Marco Caminati⁶ MD,
4 Yoon-Seok Chang⁷ MD PhD, Davide Caimmi^{1,8} MD PhD, Mario Sanchez-Borges⁹ MD PhD, Lanny
5 Rosenwasser¹⁰ MD PhD, Alain Didier^{11,12} MD PhD, Frédéric de Blay¹³ MD PhD, Jean-François Fontaine¹⁴
6 MD, Isabelle Bosse¹⁵ MD, Sebastien Lefevre¹⁶ MD, Cintia Bassani¹⁷ MD, Maria De Filippo¹⁸ MD, Igancio
7 Ansotegui¹⁹ MD PhD, Mario Morais-Almeida²⁰ MD PhD, Motohiro Ebisawa²¹ MD PhD, Bryan Martin²²
8 MD PhD, Bernard Yu-Hor Thong²³ MD PhD, Pascal Demoly^{1,8,24} MD PhD, Luciana Kase Tanno^{*1,8,24} MD
9 PhD

10

11 1. University Hospital of Montpellier, Montpellier, France

12 2. Allergy Unit, Regional University Hospital of Malaga-IBIMA-UMA-ARADyAL-BIONAND, Malaga, Spain.

13 3. Center for Drug Safety and Immunology, Department of Medicine, Vanderbilt University Medical Centre, Nashville
14 Tennessee

15 4. Vanderbilt University School of Medicine, Vanderbilt University, Nashville, Tennessee

16 5. Centre for Clinical Pharmacology and Infectious Diseases, Institute for Immunology and Infectious Diseases,
17 Murdoch University, Murdoch, Western Australia

18 6. Department of Medicine, Allergy Asthma and Clinical Immunology Section, University of Verona, Verona Italy

19 7. Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College
20 of Medicine, Seongnam 13620, Korea.

21 8. Sorbonne Université, INSERM UMR-S 1136, IPLESP, Equipe EPAR, 75013, Paris, France

22 9. Allergy and Clinical Immunology Department, Centro Médico Docente La Trinidad and Clínica el Avila, Caracas,
23 Venezuela.

24 10. Department of Pediatrics, Division of Immunology Research, Children's Mercy Hospitals & Clinics, Kansas City, MO
25 64108, USA

26 11. Pôle des Voies Respiratoires, Hôpital Larrey, CHU de Toulouse, Toulouse, France

27 12. Centre de Physiopathologie Toulouse Purpan, INSERM U1043, CNRS UMR 5282, Université Toulouse III, Toulouse,
28 France

29 13. Chest Diseases Department, University Hospital of Strasbourg, Strasbourg, France

30 14. Département des maladies allergiques et respiratoires, University Hospital of Reims, Reims, France

31 15. Syndicate of French Allergists, La Rochelle, France

32 16. Regional Institute for Allergic and Environmental diseases, Metz Regional Hospital, Metz, France

33 17. Department of Allergy and Clinical Immunology, IMED School of Medicine, Passo Fundo, Brazil

34 18. Pediatric Clinic, Fondazione IRCCS Policlinico San Matteo, and Department of Clinical, Surgical, Diagnostic and
35 Pediatric Sciences, University of Pavia, Pavia, Italy

36 19. Department of Allergy and Immunology, Hospital Quirónsalud Bizkaia Erandio, Bilbao, Spain

37 20. Allergy Center, CUF Descobertas Hospital, Lisbon, Portugal

38 21. Clinical Research Center for Allergy and Rheumatology, Sagami National Hospital, Japan

39 22. Medicine and Pediatrics, The Ohio State University in Columbus, Ohio, USA

40 23. Department of Rheumatology, Allergy and Immunology, Tan Tock Seng Hospital, Singapore

41 24. WHO Collaborating Centre on Scientific Classification Support, Montpellier, France

42

43

44 * Corresponding author: Luciana Kase Tanno MD, PhD, Division of Allergy, Department of Pulmonology, Hôpital Arnaud de Villeneuve,
45 University Hospital of Montpellier, 371, av. du Doyen Gaston Giraud - 34295, Montpellier cedex 5, France. Tel.: +33 467336107 Fax: +33
46 467633645

47 E-mail: luciana.tanno@gmail.com

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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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158 CONTRIBUTIONS:

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*).

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)
Specialty¹						
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 work¹						
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)
Recognition of Allergy as							
	<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)
Type of Biological Agent prescribed¹							
	<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)
Right of prescription of BA by allergists							
	<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)
Prescription of BA in clinical practice							
	<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)

¹respondents 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		
<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)
Allergic investigation (in vivo/in vitro tests)	21.5% (75/348)	27.5% (96/348)
Desensitization	12.3% (43/348)	18.9% (66/348)