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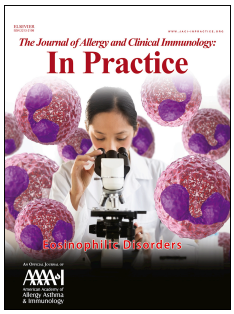

BIOLOGICAL TREATMENTS IN ALLERGY: PRESCRIBING PATTERNS AND MANAGEMENT OF HYPERSENSITIVITY REACTIONS

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PII: S2213-2198(20)31198-3

DOI: https://doi.org/10.1016/j.jaip.2020.10.044

Reference: JAIP 3221

To appear in: *The Journal of Allergy and Clinical Immunology: In Practice*

Received Date: 7 September 2020

Revised Date: 18 October 2020

Accepted Date: 22 October 2020

Please cite this article as: Barakat L, Torres MJ, Phillips EJ, Caminati M, Chang YS, Caimmi D, Sanchez-Borges M, Rosenwasser L, Didier A, de Blay F, Fontaine JF, Bosse I, Lefevre S, Bassani C, De Filippo M, Ansotegui I, Morais-Almeida M, Ebisawa M, Martin B, Yu-Hor Thong B, Demoly P, Tanno LK, BIOLOGICAL TREATMENTS IN ALLERGY: PRESCRIBING PATTERNS AND MANAGEMENT OF HYPERSENSITIVITY REACTIONS, *The Journal of Allergy and Clinical Immunology: In Practice* (2020), doi: https://doi.org/10.1016/j.jaip.2020.10.044.

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

Leyla Barakat[1]MD, Maria Jose Torres[2] MD PhD, Elizabeth J. Phillips[3,4,5]MD PhD, Marco Caminati[6] MD, Yoon-Seok Chang[7] MD PhD,Davide Caimmi[1,8] MD PhD, Mario Sanchez-Borges[9] MD PhD, Lanny Rosenwasser[10] MD PhD, Alain Didier[11,12] MD PhD, Frédéric de Blay[13] MD PhD, Jean-François Fontaine[14] MD, Isabelle Bosse[15] MD, Sebastien Lefevre[16] MD, Cintia Bassani[17] MD, Maria De Filippo[18] MD, Igancio Ansotegui[19] MD PhD, Mario Morais-Almeida[20] MD PhD, Motohiro Ebisawa[21] MD PhD, Bryan Martin[22] MD PhD, Bernard Yu-Hor Thong [23] MD PhD, Pascal Demoly[1,8,24] MD PhD, Luciana Kase Tanno*[1,8,24] MD PhD

1. University Hospital of Montpellier, Montpellier, France
2. Allergy Unit, Regional University Hospital of Malaga-IBIMA-UMA-ARADyAL-BIONAND, Malaga, Spain.
3. Center for Drug Safety and Immunology, Department of Medicine, Vanderbilt University Medical Centre, Nashville Tennessee
4. Vanderbilt University School of Medicine, Vanderbilt University, Nashville, Tennessee
5. Centre for Clinical Pharmacology and Infectious Diseases, Institute for Immunology and Infectious Diseases, Murdoch University, Murdoch, Western Australia
6. Department of Medicine, Allergy Asthma and Clinical Immunology Section, University of Verona, Verona Italy
7. Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam 13620, Korea.
8. Sorbonne Université, INSERM UMR-S 1136, IPLESP, Equipe EPAR, 75013, Paris, France
9. Allergy and Clinical Immunology Department, Centro Médico Docente La Trinidad and Clínica el Avila, Caracas, Venezuela.
10. Department of Pediatrics, Division of Immunology Research, Children's Mercy Hospitals & Clinics, Kansas City, MO 64108, USA
11. Pôle des Voies Respiratoires, Hôpital Larrey, CHU de Toulouse, Toulouse, France
12. Centre de Physiopathologie Toulouse Purpan, INSERM U1043, CNRS UMR 5282, Université Toulouse III, Toulouse, France
13. Chest Diseases Department, University Hospital of Strasbourg, Strasbourg, France
14. Département des maladies allergiques et respiratoires, University Hospital of Reims, Reims, France
15. Syndicate of French Allergists, La Rochelle, France
16. Regional Institute for Allergic and Environmental diseases, Metz Regional Hospital, Metz, France
17. Department of Allergy and Clinical Immunology, IMED School of Medicine, Passo Fundo, Brazil
18. Pediatric Clinic, Fondazione IRCCS Policlinico San Matteo, and Department of Clinical, Surgical, Diagnostic and Pediatric Sciences, University of Pavia, Pavia, Italy
19. Department of Allergy and Immunology, Hospital Quirónsalud Bizkaia Erandio, Bilbao, Spain
20. Allergy Center, CUF Descobertas Hospital, Lisbon, Portugal
21. Clinical Research Center for Allergy and Rheumatology, Sagamihara National Hospital, Japan
22. Medicine and Pediatrics, The Ohio State University in Columbus, Ohio, USA
23. Department of Rheumatology, Allergy and Immunology, Tan Tock Seng Hospital, Singapore
24. WHO Collaborating Centre on Scientific Classification Support, Montpellier, France

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

E-mail: luciana.tanno@gmail.com

KEYWORDS: “Allergy and Immunology”, “allergists”, “asthma”, “atopic eczema”, “biological therapy”, “hypersensitivity”, “allergic reaction”, “Drug-Related side effects and adverse reactions »

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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FUNDING:

Luciana Kase Tanno received an unrestricted Novartis and MEDA/Mylan Pharma grants through CHUM administration. LKT received a research AllerGOS grant.

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.

AKNOWLEDGEMENTS:

The authors thank the French Allergy Syndicate for their help disseminating the survey to their members.

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)*.

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

LIST OF FIGURES

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)

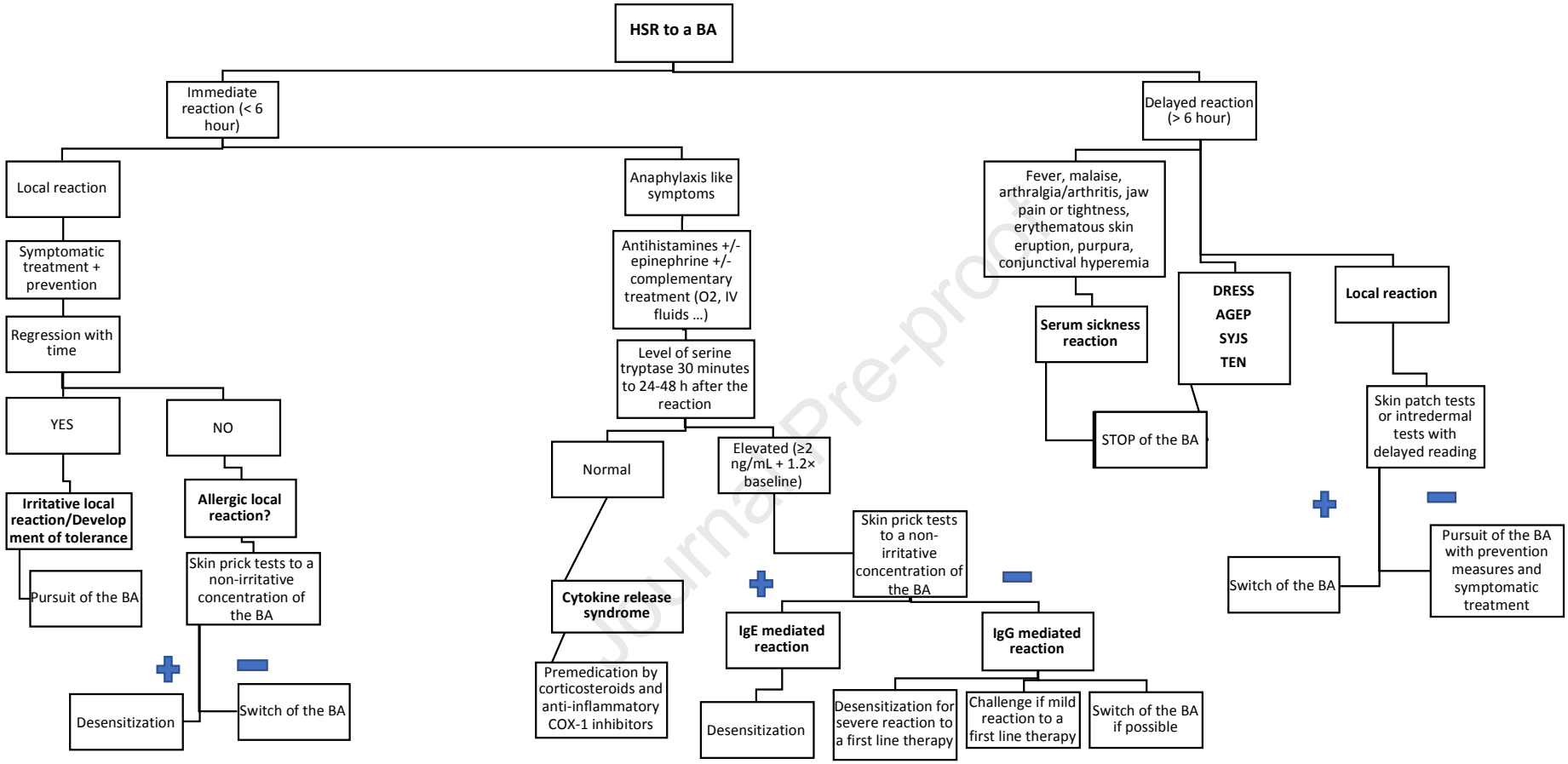

Figure E1

Online Repository Text: Survey Biological Treatments In Allergy: Prescription And Management Of Hypersensitivity Reactions (English version)

*Mandatory

1. Please indicate your age : *

2. Please indicate your gender : *

- o Male
- o Female

3. Please indicate your specialty (ies) *
Many possible responses.

- o Allergology
- o Basic science
- o Clinical Immunology
- o Dermatology
- o ENT
- o Internal medicine
- o Pediatrics
- o Pneumology
- o Ophthalmology
- o General medicine
- o Other :

4. Please indicate where you practice : *
Many possible responses.

- o Public hospital
- o Private office
- o Private hospital
- o Laboratory
- o Other :

5. Please indicate your country of practice : *

6. Please indicate if the allergy in your country is considered as : *
Many possible responses.

- o Full specialty
- o Subspescialty
- o Post graduate topic
- o Other :

7. Please indicate if allergists in your country are allowed to prescribe biological treatments : *

- o YES
- o NO
- o I don't know
- o Other :

8. Please indicate if you prescribe biological agents in your clinical practice: *

- o YES
- o NO

9. If YES, please indicate the biological agents you prescribe for allergy diseases:
Many possible responses.

- o Anti IgE (Omalizumab)
- o Anti IL5 (Mepolizumab, Reslizumab)
- o Anti IL13R-IL4R (Dupilumab)
- o Anti IL-5R (Bentalizumab)
- o IL-1 antagonists (anakinra, canakinumab, rilonacept)
- o TNF alpha antagonists (Infliximab, Etanercept, Adalimumab…)
- o Anti CD20 (RITUXIMAB, …)
- o Other :

10. If YES, please indicate on which frequency basis per week you prescribe biotherapies:

- o ≤1
- o 2-5
- o 5-10
- o >10

11. The expenses of the treatments with biological agents prescribed for allergic and hypersensitivity conditions are : *
Many possible responses.

- o Completely covered by the national security
- o Partialy covered by the national security
- o Completely covered by the private security
- o Partialy covered by the private security
- o Part of research protocols or clinical trials
- o Completely covered by the patient
- o I don’t know
- o Other :

12. Please specify the most common hypersensitivity reactions you encounter with the biological agents you prescribe : *
Many possible responses.

- o Local reaction
- o Anaphylaxis like symptoms
- o Delayed exanthemas
- o Severe cutaneous reactions (DRESS, Stevens Johnsons…)
- o Other :

13. Please indicate if you follow specific guidelines regarding the hypersensitivity reactions you encounter to biotherapies : *
Many possible responses.

- o National recommandations
- o Local/structure recommandations
- o Literature
- o Personal experience
- o Other :

14. For mild to moderate hypersensitivity reactions to a biological agent, please indicate which actions you carry out:
Many possible responses.

- o Pursue the same biotherapy and treat the reaction symptomatically
- o Switch of the biotherapy
- o Stop the biotherapy and carry on with non-biological treatment
- o In vivo and/or in vitro investigation to confirm the imputability
- o Desensitization
- o Other :

15. For moderate to severe hypersensitivity reactions, please indicate which actions you carry out:
Many possible responses.

- o Pursue the same biotherapy and treat the reaction symptomatically
- o Switch of the biotherapy
- o Stop the biotherapy and carry on with non-biological treatment
- o In vivo and/or in vitro investigation to confirm the imputability
- o Desensitization
- o Other :

16. Please indicate if you notice a relation between the occurrence of immunological adverse reactions and the presence of atopy background : *

- o YES
- o NO
- o Other :

17. Please indicate if you report these adverse reactions : *

- o YES
- o NO

18. If you replied YES for the last question, please indicate to which agency do you report:
Many possible responses.

- o Institutional pharmacovigilance
- o National pharmacovigilance
- o Non-governamental bodies
- o Other :