

CORRESPONDENCE

Rapid desensitization to chemotherapy and monoclonal antibodies is effective and safe

DOI:10.1111/all.12228

We would like to acknowledge Madrigal-Burgaleta et al. (1) for their wonderful report on rapid desensitization (RD) to antineoplastic drugs, with the description of 189 desensitizations performed in 23 patients. Continued reports on the safety and efficacy of RD to drugs emerging from different institutions are essential to allow the dissemination of desensitization programmes. The authors' RD protocol is not novel, being based on the Brigham and Women's Hospital/Dana Farber Cancer Institute (BWH/DFCI) desensitization protocol (2, 3), with fewer steps and higher starting dose, which may not be applicable universally to high-risk patients. Faster desensitization protocols in immediate and delayed drug hypersensitivity reactions have exhibited higher risks and failure rates (4, 5).

The starting dose of the Madrigal-Burgaleta et al. protocol is 80-fold higher than the one used in the 12-step BWH/DFCI protocol and is equivalent to its step 7 (2, 3). In a cohort of 98 patients desensitized with the BWH/DFCI protocol, of which 80% had a severe initial reaction, 25% of all reactions induced by desensitization occurred during the first 8 steps, highlighting the potential risks of higher starting doses (2). Also, despite the use of different grading systems for assessing the severity of immediate HSRs between the two studies, it could be argued that a higher percentage of patients with severe initial reactions were included in the BWH/DFCI series (80%) compared with the present study in which 30% were considered to have had a severe reaction. Madrigal-Burgaleta et al. used a grading system based on the 'Common Terminology Criteria for Adverse Events' guidelines developed to describe adverse drug reactions induced by chemotherapy in patients with cancer, whereas the BWH/DFCI studies used the classification proposed by Brown (6). In this light, further data are needed before the modifications made to the BWH/DFCI protocol by Madrigal-Burgaleta et al. can be considered safe for all patients with HSRs to antineoplastic drugs. The recent EAACI position paper of the Drug Allergy Interest Group includes as future needs for improving drug desensitization (5): (i) multicenter clinical trials with standardized and well-characterized patients; (ii) comparison of different protocols in one well-characterized patient group and comparison of one protocol in various, well-characterized patient groups.

Although the authors suggest starting with higher doses, they also state that more dilute initial doses could be used, depending on skin test endpoint titration. However, the predictive values of skin tests to antineoplastic drugs were

not determined, and, currently, studies outcomes and consensus support the use of more dilute starting solutions in all RD, despite the higher total time of administration (2–4). The authors showed that 70% of their patients with negative skin tests to oxaliplatin who undergone controlled provocation had positive challenges, indicating a poor predictive value for oxaliplatin skin testing. Although other reports indicate a higher rate of positive skin test to oxaliplatin, the true predictive value of a negative skin test is not available (7). As suggested by the authors, recent preliminary data with oxaliplatin-specific serum IgE indicate that *in vitro* testing could be a very promising complementary diagnostic tool for the identification of allergic patients (7).

It should be emphasized that the BWH/DFCI desensitization protocol complies with safety measures for hazardous drug handling. The tubing of each bag is primed by pharmacy with the antineoplastic drug and is equipped with a connecting device that prevents any contact with the drug. The system is then connected to a running saline line in close proximity to the patient, allowing delivery of small volumes during the initial steps of desensitization (2, 3). This method avoids unnecessary priming steps with saline that prolongs and interrupts desensitization.

Desensitization has become a cornerstone in the management of immediate hypersensitivity reactions (HSRs) to chemotherapy and monoclonal antibodies among other medications. It is the only effective procedure for overcoming HSRs to first-line therapy, thus representing an important advance in patients' treatment and prognosis. This initially empiric procedure is now supported by *in vivo* and *in vitro* evidence (2, 3, 8) and we thank Madrigal-Burgaleta et al. for providing further evidence of its efficacy.

Author contributions

All authors meet the three conditions:

- 1 Substantial contributions to conception of the correspondence.
- 2 Drafting the article and revising it critically for important intellectual content.
- 3 Final approval of the version to be published.

Conflict of interest

No conflict of interest exists regarding the publication of this article.

P. Giavina-Bianchi¹, J. Caiado², M. Picard³, L. Pur Ozyigit⁴,
V. Mezzano⁵ and M. Castells⁶

¹Clinical Immunology and Allergy Division, University of São Paulo, São Paulo, Brazil;

²Department of Immunoallergy, Hospital de Santa Maria/ Centro Hospitalar Lisboa Norte, Lisbon, Portugal;

³Department of Medicine, Division of Allergy and Immunology, Hôpital Maisonneuve-Rosemont, Université de Montréal, Montreal, QC, Canada;

⁴Department of Allergy and Immunology, American Hospital, Istanbul, Turkey;

⁵Department of Clinical Immunology and Rheumatology, Pontificia Universidad Católica de Chile, Santiago, Chile;

⁶Department of Medicine, Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
E-mail: pbianchi@usp.br

References

1. Madrigal-Burgaleta R, Berges-Gimeno MP, Angel-Pereira D, Ferreira-Monteagudo R, Guillen-Ponce C, Pueyo C et al. Hypersensitivity and desensitization to antineoplastic agents: outcomes of 189 procedures with a new short protocol and novel diagnostic tools assessment. *Allergy* 2013;**68**:853–861.
2. Castells MC, Tennant NM, Sloane DE, Ida Hsu F, Barrett NA, Hong DI et al. Hypersensitivity reactions to chemotherapy: outcomes and safety of rapid desensitization in 413 cases. *J Allergy Clin Immunol* 2008;**122**: 574–580.
3. Brennan PJ, Rodriguez Bouza T, Hsu FI, Sloane DE, Castells MC. Hypersensitivity reactions to mAbs: 105 desensitizations in 23 patients, from evaluation to treatment. *J Allergy Clin Immunol* 2009;**124**:1259–66.
4. Cernadas JR, Brockow K, Romano A, Aberer W, Torres MJ, Bircher A et al. General considerations on rapid desensitization for drug hypersensitivity – a consensus statement. *Allergy* 2010;**65**:1357–1366.
5. Scherer K, Brockow K, Aberer W, Gooi JHC, Demoly P, Romano A et al. Desensitization in delayed drug hypersensitivity reactions – an EAACI position paper of the Drug Allergy Interest Group. *Allergy* 2013;**68**:844–852.
6. Brown SGA. Clinical features and severity grading of anaphylaxis. *J Allergy Clin Immunol* 2004;**114**:371–376.
7. Caiado J, Pereira-Santos M, Venenalm L, Costa L, Pedro E, Barbosa M et al. *In vitro* diagnosis in hypersensitivity to platins [Abstract]. *Allergy* 2011;**66**(Suppl. 94):5–6.
8. Sancho-Serra MDC, Simarro M, Castells M. Rapid IgE desensitization is antigen specific and impairs early and late mast cell responses targeting FcεRI internalization. *Eur J Immunol* 2011;**41**:1004–1013.

REPLY

We would like to thank Giavina-Bianchi et al. for their comments on our recent publication (1). Several issues are brought out, and we would like to briefly clarify some key points:

- 1 Regarding starting dose: In the hands of our Desensitization Program (equipped with specific resources, expert personnel, and a special area for these therapeutic techniques), the Ramon y Cajal University Hospital (RCUH) Rapid Desensitization (RD) standard protocol showed a very good safety profile in our population (1). Breakthrough-reactions during the infusion of solution A (steps 1–4) were only observed in 0.5% of 189 desensitizations (one patient suffered two reactions during the infusion of solution A of a first desensitization). We encourage Giavina-Bianchi (Brazil), Caiado (Portugal), Picard (Canada), Pur Ozyigit (Turkey) and Mezzano (Chile) to publish their own data, placing an emphasis on their different populations, experiences and practical approaches.
- 2 Skin test endpoint-titration is a cornerstone in the daily practice of any allergist, and its use is specifically taken into account in a recent consensus statement on rapid desensitization for drug hypersensitivity endorsed by the European Network of Drug Allergy and the European Academy of Allergy and Clinical Immunology Interest Group on drug hypersensitivity (2).

- 3 Giavina-Bianchi et al. suggest that the priming steps with dilutor substance prolong and interrupt desensitization. To our knowledge, there are no published data to support this assertion. Our published data demonstrated the short 10-step RCUH RD standard protocol to be effective and safe in our population, with objective after-desensitization skin tests negativization (supporting the fact that the desensitization is correctly achieved). Priming steps with dilutor substance are one of the key issues for the RCUH RD standard protocol to comply with our institutional requirements for handling hazardous drugs. Priming tubes with hazardous agents and using special devices to avoid contact with the drug are valid measures which, however, may be not always allowed at many institutions, due either to safety local requirements or to time-availability at the pharmacy, for example. Therefore, other institutions may encounter similar local problems, and may thus find our approach to antineoplastic hypersensitivity a useful tool for their desensitization programs.

Our framework for our daily work is: thinking globally, and acting locally (by means of a multifaceted and multidisciplinary approach), focusing on continual improvement and process optimization strategies. Our cornerstones regarding this topic are: to identify high-risk patients is a must, to understand that some patients may need a tailor-made plan, and to take into account diagnostic Gold Standard should be

Graded Challenge (whenever possible, according to risk stratification) prior to the indication of desensitization.

Once all the previous matters have been clarified, we summarize by highlighting: 10-step RCUH RD standard protocol has been successfully used for different drugs (oxaliplatin, carboplatin, paclitaxel, docetaxel, cyclophosphamide and rituximab) and for different types of immediate reactions (IgE-dependent and IgE-independent) with an excellent safety profile (and improved compliance with our institutional hazardous drugs handling guidelines) in a significant number of patients from our population, allowing for single-morning desensitizations (approximately 4 h). Additionally, we present a specific practical approach other groups may adopt for their local populations, and we report the first important series of desensitizations to oxaliplatin, along with cutting-edge data on a novel diagnostic tool for these patients: oxaliplatin-specific IgE determination.

‘Eppur si muove’, Galileo Galilei (3).

References

1. Madrigal-Burgaleta R, Berges-Gimeno MP, Angel-Pereira D, Ferreiro-Monteagudo R, Guillen-Ponce C, Pueyo C et al. Hypersensitivity and desensitization to antineoplastic agents: outcomes of 189 procedures with a new short protocol and novel diagnostic tools assessment. *Allergy* 2013;**68**:853–861.
2. Cernadas JR, Brockow K, Romano A, Aberer W, Torres MJ, Bircher A et al. General considerations on rapid desensitization for drug hypersensitivity – a consensus statement. *Allergy* 2010;**65**:1357–1366.
3. Baretti GMA. *The Italian Library. Containing An Account of the Lives and Works of the*

Most Valuable Authors of Italy. With a Preface, Exhibiting The Changes of the Tuscan Language, from the barbarous Ages to the present Time. London: Printed for A. Millar, 1757.

Author contributions

All of the authors, in agreement with all co-authors of the original article, have contributed to the design of the article, and/or to the interpretation of data, and/or to the drafting and critical revision of the article for important intellectual content, and/or to the final approval of the version to be published of this reply letter.

Conflicts of interest

There are no potential conflicts of interest for any of the authors regarding this article. There are no financial interests.

E. Alvarez-Cuesta, R. Madrigal-Burgaleta, M. P. Berges-Gimeno and D. Angel-Pereira
Allergy Division, Ramon y Cajal University Hospital,
Madrid, Spain
E-mail: ealvarezcuesta@gmail.com

Diversity of allergens contained in dog saliva

DOI:10.1111/all.12264

Most individuals sensitized to cats react to Fel d 1, and standardized extracts are based on particular concentrations of this allergen. In contrast, a distinctive major dog allergen recognized by the specific IgE of dog-sensitized individuals has not been identified. Several dog allergens, including Can f 1, Can f 2, and Can f 3, have been traditionally considered relevant to particular individuals sensitized to dogs, with Can f 2 (lipocalin) and Can f 3 (albumin) being responsible for cross-reactivity among mammals. More recently, other dog allergens (Can f 4, Can f 5, and Can f 6) have been identified and proven clinically relevant to particular individuals and also responsible for cross-reactivity among species (1–3).

Mammalian allergens can occur in a variety of sources, and different raw materials are used for the production of allergenic extracts. These materials include dander, hair, epithelium, pelt, skin scrapings, and hides. Dog raw materials differ in allergenic composition, with dander containing greater Can f 1 concentrations than epithelia. Dander is the

most common material used for the preparation of dog allergenic extracts.

The fact that no major clinically relevant dog allergens that affect most sensitized individuals exist, combined with the heterogenic composition of dog raw materials, is responsible for the presence of a number of products in the market with differential diagnostic value. Standardized allergenic extracts for immunotherapy are lacking.

In the May issue of *Allergy*, Polovic et al. (4) described the interesting finding that dog saliva contains allergens, not previously identified in dander, and suggested that saliva could have an increased diagnosis potential, compared with other materials. The authors of this article collected saliva samples from 14 individual dogs belonging to 11 different breeds and compared their allergenic content with that measured in a dog dander sample commercially obtained.

As expected, a large variation of different allergen concentrations was detected between individual dogs, and the authors propose that particular dog breeds could be less