A Pilot Experience Using a 1-Bag Intravenous Rapid Desensitization Protocol for Chemotherapy and Biologics in a Cohort of Patients With Access to a Delabeling Pathway

Vázquez-Revuelta P[1,2,3], Lleonart-Bellfill R[1,2,3], Molina-Mata K[1,4], Muñoz-Sánchez C[1,5], Rey-Salido M[1,5], Madrigal-Burgaleta R[1,6]

[1]*Drug Desensitisation Centre, Catalan Institute of Oncology (Institut Català d'Oncologia – ICO), Barcelona, Spain*

[2]*Allergy Department, Hospital Universitari de Bellvitge, Barcelona, Spain*

[3]*Institut d'Investigació Biomèdica de Bellvitge - IDIBELL, Barcelona, Spain*

[4]*Medical Oncology Department, Catalan Institute of Oncology (Institut Català d'Oncologia – ICO), Barcelona, Spain*

[5]*Pharmacy Department, Catalan Institute of Oncology (Institut Català d'Oncologia – ICO), Barcelona, Spain*

[6]*Allergy & Severe Asthma Service, St Bartholomew's Hospital, Barts Health NHS Trust, London, UK*

J Investig Allergol Clin Immunol 2023; Vol. 33(4): 289-291
doi: 10.18176/jiaci.0860

Key words: Drug allergy. Delabeling. Drug challenge. Desensitization. Personalized medicine.

Palabras clave: Alergia medicamentosa. Desetiquetado de alergia. Provocación controlada medicamentosa. Desensibilización. Medicina personalizada.

Patients who experience drug hypersensitivity reactions (DHRs) to chemotherapy or biologics benefit from assessment by expert allergists, who have access to the resources, techniques, and diagnostic pathways necessary for delabeling patients (thereafter considered nonallergic) [1]. In the case of confirmed hypersensitivity, rapid drug desensitization (RDD) enables allergists to help affected patients continue their first-choice treatment [1]. RDD is a cost-effective technique that induces temporary tolerance to the culprit drug to maintain survival outcomes in reactive patients [2,3].

RDD protocols for chemotherapy and biologics validated in large cohorts of patients use 3 bags with increasing drug concentrations [3-5]. However, recent articles suggest that optimized 1-bag protocols might have specific benefits, such as minimizing human error by streamlining procedures, decreasing the chances of chemotherapy spills by eliminating bag changes, shortening preparation times by cutting down on the number of dilutions, and avoiding drug dilutions to concentrations below those accepted in the manufacturer's recommendations [5-9].

This pilot study aims to assess the feasibility of a 1-bag intravenous RDD protocol for chemotherapy and biologics in our cohort of well-characterized patients (ie, after a diagnostic pathway including confirmatory drug challenge testing).

We conducted a single-center, prospective, longitudinal, observational study, which was approved by the local ethics committee. We included patients referred to our drug desensitization center over 1 year. The exclusion criteria were nonimmediate DHRs, lack of consent, and drug administration routes other than the intravenous route.

We graded the severity of the initial reactions according to the Ramon y Cajal University Hospital (RCUH) classification [5] and the Brown classification [10]. Endophenotypes were defined as per recent consensus [1]. In addition, skin testing, including skin prick testing (SPT) and intradermal testing (IDT), was performed as per the European Academy of Allergy and Clinical Immunology (EAACI) standards [11,12] (see Supplementary Table 1 for more information on skin testing).

Patients underwent a thorough risk assessment [13] before being stratified into low-, medium-, and high-risk groups according to a classification devised by our group (Table).

We offered drug challenges with the culprit drug to those patients we considered to have a favorable risk assessment (ie, low-risk and medium-risk patients with negative or equivocal skin testing results). In addition, concomitant drugs (eg, other chemotherapy or biological agents, leucovorin, or antiemetics administered simultaneously or before the culprit drug) that could be involved in the reaction were studied separately using skin testing and drug challenge [1,14].

We followed EAACI recommendations for drug challenge with chemotherapy and biologics [11,12]. Patients with a negative drug challenge result were considered nonallergic and, thus, delabeled of their hypersensitivity.

We offered RDD to patients with confirmed hypersensitivity (ie, positive skin test or drug challenge result). We also considered for RDD those patients who could not undergo confirmatory challenge because of their unfavorable risk assesment. The study flow chart in Supplementary Figure 1 shows the management pathways.

A recent consensus document discussed the fundamental requisites that RDD protocols should meet, based on in vitro findings and in vivo data from large cohorts of patients [1]. In a nutshell, an RDD protocol should use around 10-16 steps to administer increasingly higher subthreshold doses, which double (approximately) every 15-30 minutes, starting at a 1000-10 000th part of the target dose [1]. Thus, we designed a standard, flexible (enabling personalization), 1-bag RDD protocol meeting these requirements (see Supplementary Table 2 for a practical example).

In the event of a breakthrough reaction during RDD, we personalized management, as described in a recent article [5]. In addition, we reassessed reactive patients based on in vivo and in vitro biomarkers and made personalized adjustments

Table. Stratification of Risk Into Low-, Medium-, and High-Risk Patients as per the ICO-HUB Scale.

High-Risk Criteria
Severe initial reaction (grade 3 Brown or grade 3-4 RCUH)
Positive skin prick testing
Positive intradermal test + major risk factor regardless of severity of initial reaction
REMA score ≥ 2
Medium-Risk Criteria
Mild initial reactions (grade 1 Brown and RCUH) + major risk factor
Negative skin testing + moderate initial reaction (grade 2 Brown & RCUH)
Mild or moderate initial reactions (grade 1 or 2) + positive/equivocal intradermal testing + no major risk factors
Low-Risk Criteria
Mild initial reactions (grade 1 Brown and RCUH) + negative skin test + no major risk factors
Major Risk Factors
The patient is not well enough to withstand anaphylaxis or has comorbidities that might trigger a situation beyond medical control
FEV_1 <1 L or <80%
Initial reaction grade 4 RCUH (shock)
Significantly raised tryptase during the reaction (compared to baseline)
Age >75 years
Unavoidable intake of ß-blockers or ACEIs
Cognitive impairment, sensory impairment, language barrier, or difficulty identifying and communicating a reaction
Skin testing performed before 4 weeks (theoretical risk of false negatives)
Criteria For Immediate Reactions
Reactions with features of type I Gell and Coombs reactions[a] (or CRR) occurring during the drug infusion or within 1-6 h after the last drug administration
Criteria For Nonimmediate Reactions
Reactions with features of type II-IV Gell and Coombs reactions[a] (or CRR) at any time as from 1 h after from the initial drug administration

Abbreviations: ACEI, angiotensin-converting-enzyme inhibitor; CRR, cytokine release reaction;FEV1, forced expiratory volume in 1 second; HUB, Bellvitge University Hospital, Barcelona, Spain; ICO, Catalan Institute of Oncology, Barcelona, Spain; REMA score, Spanish Network on Mastocytosis score; RCUH, Ramón y Cajal University Hospital.
[a]In our study, type I Gell and Coombs reactions include both IgE-mediated and non-IgE-mediated reactions, as per World Allergy Organization recommendations (see reference No 1).

to the second RDD (eg, customized premedication or prophylactic drugs, decelerating dose-escalation, or additional solutions) [1,5].

We performed both drug challenge and RDD in a dedicated allergy-led area within the hospital's infusion center, which is equipped with all the necessary resources for anaphylaxis, including rapid access to intensive care, a 1:2 nurse:patient ratio (nurses trained in both drug allergy and oncology), and an allergist at the bedside, as per standard recommendations [1,4,11,12].

Ninety patients met the inclusion criteria during this 1-year pilot study (see Supplementary figure 1 for further information). All patients could continue their first-choice treatment either by delabeling their allergy or by RDD. Of all the patients referred, 25 (28%) were delabeled after a negative drug challenge to all the drugs involved in the reaction. The remaining 65 patients received their medications through RDD.

We performed 263 RDDs in 65 patients using our 1-bag RDD protocol. All RDDs were successful, as all desensitized patients received their target dose (see Supplementary Figure 2 for futher data).

This pilot study shows that our 1-bag RDD protocol is effective and safe in administering chemotherapy and biologics to reactive patients. Most procedures (79%) were uneventful, and there were only 2 severe (grade 3) reactions. No patients died.

We previously validated our delabeling pathway, which helped reduce the number of unnecessary RDDs in nonallergic patients [14,15]. Indeed, drug challenge was essential for delabeling patients who were not hypersensitive and ensured that they could continue with regular infusions, saving approximately 100 RDD procedures in 1 year (see Supplementary Figure 1).

All patients underwent drug challenge with concomitant drugs involved in their chemotherapy regimen. Interestingly, 1 patient was allergic to concomitant calcium folinate but not to the culprit, oxaliplatin, thus highlighting the recognized importance of a systematic approach [1,5,13].

The reaction rate is similar to that reported in previous publications, although the percentage of reactive patients (52%)

was higher than the usual 39%-42% reported elsewhere [1,3,5]. As seen in Supplementary figure 2 (vignette k.4a), this was primarily due to reactions with platins. Many were quickly self-limiting and did not even warrant stopping the procedure (mostly pruritus or isolated throat tightness/tingling, a known adverse effect). We expect our future data to clarify whether this is relevant to the 1-bag protocol or simply due to disparities in data collection.

Other groups have reported their experiences with similar 1-bag RDD protocols [6-9]. Unfortunately, comparing results is difficult owing to population and methodological differences. Nevertheless, when adjusted to the same target dose and bag concentration, these 3 protocols follow similar design rules and differ from each other only slightly. The relevance of these differences remains unknown.

RDD protocols cannot be evaluated in isolation. In our experience, multidisciplinary work, access to dedicated spaces/resources, patient selection and personalization, adjustments by expert allergists, and adequate biomarkers and risk assessment tools were equally essential as protocol design for ensuring safety [1,4].

In conclusion, our pilot study validates the 1-bag RDD protocol for use in a population of well-characterized patients, including severe reactors, patients with different endophenotypes, and patients receiving various drugs. These promising results warrant a more extensive study.

Funding

The authors declare that they have no conflicts of interest.

Conflicts of Interest

This work was supported by IDIBELL (Institut d'Investigació Biomèdica de Bellvitge) and the CERCA (Centres de Recerca de Catalunya) Institute – Generalitat de Catalunya.

References

1. Alvarez-Cuesta E, Madrigal-Burgaleta R, Broyles AD, Cuesta-Herranz J, Guzman-Melendez MA, Maciag MC, et al. Standards for Practical Intravenous Rapid Drug Desensitization & Delabeling: A WAO Committee Statement. World Allergy Organization J. 2022;15(6):100640.
2. Berges-Gimeno MP, Carpio-Escalona LV, Longo-Munoz F, Bernal-Rubio L, Lopez-Gonzalez P, Gehlhaar P, et al. Does Rapid Drug Desensitization to Chemotherapy Affect Survival Outcomes? J Investig Allergol Clin Immunol. 2020;30(4):254-63.
3. Sloane D, Govindarajulu U, Harrow-Mortelliti J, Barry W, Hsu FI, Hong D, et al. Safety, Costs, and Efficacy of Rapid Drug Desensitizations to Chemotherapy and Monoclonal Antibodies. J Allergy Clin Immunol Pract. 2016;4(3):497-504.
4. Hong DI, Madrigal-Burgaleta R, Banerji A, Castells M, Alvarez-Cuesta E. Controversies in Allergy: Chemotherapy Reactions, Desensitize, or Delabel? J Allergy Clin Immunol Pract. 2020;8(9):2907-15 e1.
5. Madrigal-Burgaleta R, Bernal-Rubio L, Berges-Gimeno MP, Carpio-Escalona LV, Gehlhaar P, Alvarez-Cuesta E. A Large Single-Hospital Experience Using Drug Provocation Testing and Rapid Drug Desensitization in Hypersensitivity to Antineoplastic and Biological Agents. J Allergy Clin Immunol Pract. 2019;7(2):618-32.
6. Sala-Cunill A, Molina-Molina GJ, Verdesoto JT, Labrador-Horrillo M, Luengo O, Galvan-Blasco P, et al. One-Dilution Rapid Desensitization Protocol to Chemotherapeutic and Biological Agents: A Five-Year Experience. J Allergy Clin Immunol Pract. 2021;9(11):4045-54.
7. Kim HH, Seo J, Ahn YH, Kim H, Yoon J-E, Suh JH, et al. Analysis of Breakthrough Reactions in 1,143 Desensitization Procedures in a Single Tertiary Hospital Using a One-Bag Desensitization Protocol. Front Allergy. 2022;3:786822.
8. Lee JH, Moon M, Kim YC, Chung SJ, Oh J, Kang DY, et al. A One-Bag Rapid Desensitization Protocol for Paclitaxel Hypersensitivity: A Noninferior Alternative to a Multi-Bag Rapid Desensitization Protocol. J Allergy Clin Immunol Pract. 2020;8(2):696-703.
9. Perez-Rodriguez E, Martinez-Tadeo JA, Perez-Rodriguez N, Hernandez-Santana G, Callero-Viera A, Rodriguez-Plata E, et al. Outcome of 490 Desensitizations to Chemotherapy Drugs with a Rapid One-Solution Protocol. J Allergy Clin Immunol Pract. 2018;6(5):1621-7 e6.
10. Brown SG. Clinical features and severity grading of anaphylaxis. J Allergy Clin Immunol. 2004;114(2):371-6.
11. Pagani M, Bavbek S, Alvarez-Cuesta E, Berna Dursun A, Bonadonna P, Castells M, et al. Hypersensitivity reactions to chemotherapy: an EAACI Position Paper. Allergy. 2022;77:388-403.
12. Bavbek S, Pagani M, Alvarez-Cuesta E, Castells M, Dursun AB, Hamadi S, et al. Hypersensitivity reactions to biologicals: An EAACI position paper. Allergy. 2022;77:39-54.
13. Madrigal-Burgaleta R, Vazquez-Revuelta P, Marti-Garrido J, Lleonart-Bellfill R, Ali FR, Alvarez-Cuesta E. Medical algorithm: Diagnosis and treatment of hypersensitivity reactions to cancer chemotherapy. Allergy. 2021;76(8):2636-40.
14. Vazquez-Revuelta P, Marti-Garrido J, Molina-Mata K, Lleonart-Bellfill R, Rey-Salido M, Madrigal-Burgaleta R. Delabeling patients from chemotherapy and biologics allergy: Implementing drug provocation testing. J Allergy Clin Immunol Pract. 2021;9(4):1742-5 e1.
15. Marti-Garrido J, Vazquez-Revuelta P, Lleonart-Bellfill R, Molina-Mata K, Munoz-Sanchez C, Madrigal-Burgaleta R. Pilot Experience Using Drug Provocation Testing for the Study of Hypersensitivity to Chemotherapy and Biological Agents. J Investig Allergol Clin Immunol. 2021;31(2):166-8.

Manuscript received May 9, 2022; accepted for publication September 6, 2022.

Ricardo Madrigal-Burgaleta
Allergy & Severe Asthma Service
4th Floor, King George V Building
St Bartholomew's Hospital, Barts Health NHS Trust
West Smithfield
London
EC1A 7BE
United Kingdom

