A pilot experience using a one-bag intravenous rapid desensitization protocol for chemotherapeutics and biologics in a cohort of patients with access to a delabeling pathway

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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 to delabel these patients as nonallergic [1]. Moreover, allergists can help those with a confirmed hypersensitivity continue their first-choice treatment thanks to rapid drug desensitization(RDD)(1). RDD is a cost-effective technique that induces temporary tolerance to the culprit drug to maintain survival outcomes in reactive patients [2,3].

Those RDD protocols for chemotherapy and biologics validated in large cohorts of patients use three bags with increasing drug concentrations [3-5]. However, recent articles suggest that optimized one-bag protocols might have specific benefits: minimizing human mistakes 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 using a one-bag intravenous RDD protocol for chemotherapy and biologics in our cohort of well-characterized patients (i.e. after a diagnostic pathway including confirmatory drug challenge testing).

We conducted a unicentric, prospective, longitudinal, observational study approved by our local Ethics Committee. We included the patients referred to our drug desensitization center for one year. Exclusion criteria were nonimmediate DHRs, lack of consent, and drug administration routes different to intravenous.

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We graded the severity of the initial reactions according to the Ramon y Cajal University Hospital(RCUH) classification and classification by Brown [5,10]. Endophenotypes were defined as per recent consensus [1]. In addition, skin testing(ST), 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 **Supplemental Table 1** for more information on ST.

Patients underwent a thorough risk-assessment [13]. Then, we stratified them into low-, medium-, and high-risk groups according to a classification devised by our group(**Table 1**).

We offered drug challenges(DC) with the culprit drug to those patients we considered to have a favorable risk-assessment (i.e., low-risk and medium-risk patients with negative or equivocal ST results). In addition, concomitant drugs (e.g. 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 with ST and DC [1,14].

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

We offered RDD to patients with a confirmed hypersensitivity (i.e., positive ST or DC). We also considered for RDD those patients who could not undergo confirmatory challenge because of their unfavorable risk-assesment. See the study flow chat in **Supplemental Figure 1** for a graphic explanation of the management pathways.

A recent consensus document discussed how *in vitro* findings combined with *in vivo* data in large cohorts have been essential in identifying the fundamental requisites for RDD protocols [1]. In a nutshell, an RDD protocol should use around 10-16 steps to administer increasingly higher subthreshold doses, which approximately double every 15-30 minutes, starting at a 1,000-10,000th of the target dose [1]. Thus, we designed a standard, flexible (allowing personalization), one-bag RDD protocol meeting these requirements (see **Supplemental Table 2** for a practical example).

In the event of a breakthrough reaction(BTR) 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 to the second RDD (e.g. customized premedication or prophylactic drugs, decelerating dose-escalation, or additional solutions) [1,5].

We performed both DC 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

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intensive care, a 1:2 nurse:patient ratio (nurses trained both in 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 one-year pilot study(see **supplemental figure 1** for further information). All patients could continue their first-choice treatment either by delabeling their allergy or by RDD. Of all referred patients, 28%(25/90) patients were delabeled after a negative DC 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 one-bag RDD protocol. All RDDs were successful, as all desensitized patients received their target dose. See **Supplementary Figure 2** for further data.

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

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

All patients underwent DC with concomitant drugs involved in their chemotherapy scheme. Interestingly, one patient was allergic to the concomitant calcium folinate and not to the culprit oxaliplatin, highlighting the recognised importance of a systematic approach [1,5,13].

The reaction rate is similar to previous publications, but the percentage of reactive patients (52%) was higher than the usual 39-42% of other articles [1,3,5]. As seen in **supplemental 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 side effect). We expect our future data to clarify whether this is relevant to the one-bag protocol or simply due to data-collection disparities.

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

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

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

Conflict of interest statement

There are no potential conflicts of interest for any of the authors regarding this article. There are no financial interests, and there have been not any provision of study materials by their manufacturer for free or at a discount from current rates.

Disclaimer

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Table. Risk stratification in low-, medium-, and high-risk patients as per ICO-HUB scale

HIGH-RISK CRITERIA

Severe initial reaction (grade 3 Brown or grade 3-4 RCUH)
Positive skin prick testing
Positive intradermal testing **+** important risk factor* regardless of severity of initial reaction
REMA score ≥ 2

MEDIUM-RISK CRITERIA

Mild initial reactions (grade 1 Brown & RCUH) **+** important 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 important risk factors*

LOW-RISK CRITERIA

Mild initial reactions (grade 1 Brown & RCUH) **+** negative skin testing **+** no important risk factors*

IMPORTANT RISK FACTORS*

The patient is not well enough to withstand anaphylaxis or comorbidities that might trigger a situation beyond medical control
FEV1 <1L or <80%
Initial reaction grade 4 RCUH (shock)
Significantly raised tryptase during the reaction (compared to baseline)
Age >75 years old
Unavoidable intake of Beta-blockers or ACEIs
Cognitive impairment, sensory impairment, language barrier, or difficulty identifying and communicating a reaction
Skin testing performed before four weeks (theoretical risk of false negatives).

CRITERIA FOR IMMEDIATE REACTIONS

Those reactions with features of type I Gell and Coombs reactions (or CRR) occurring during the drug infusion or within 1-6 hours after the last drug administration

CRITERIA FOR NONIMMEDIATE REACTIONS

Those with features of type II-IV Gell and Coombs reactions(or CRR) at any time as from 1 hour after from the initial drug administration

LEGEND: ICO, Catalan Institute of Oncology, Barcelona, Spain; HUB, Bellvitge University Hospital, Barcelona, Spain; REMA score, Spanish Network on Mastocytosis score; L, liter; FEV1, forced expiratory volume in 1 second; ACEI, angiotensin-converting-enzyme inhibitors; CRR, cytokine release reactions. In our study, type I Gell and Coombs reactions include both IgE-mediated and non-IgE-mediated reactions, as per WAO recommendations (see reference No 1).