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ORIGINAL RESEARCH

Safety and Outcomes of Rapid Drug Desensitization to Various Biologic Agents: A Multidisciplinary Experience

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Background: Biologic agents are widely used in clinical practice, but hypersensitivity reactions (HSRs) may limit their use. Rapid drug desensitization (RDD) allows patients to safely continue essential therapy by inducing temporary tolerance, but evidence on newer biologics such as daratumumab, brentuximab vedotin, and pertuzumab remains scarce.

Methods: We retrospectively reviewed 11 patients who underwent RDD for biologic-induced HSRs between 2020 and 2024 at a tertiary allergy center. Each protocol was jointly designed by an experienced allergist and clinical pharmacist and carried out in the intensive care unit under close nurse and physician supervision. Demographic, clinical, and laboratory data, reaction grades, skin test results, premedication regimens, and breakthrough reactions (BTRs) were analyzed.

Results: A total of 43 RDD cycles were performed for rituximab (n = 18), brentuximab vedotin (n = 13), daratumumab (n = 9), and pertuzumab (n = 3). Six patients underwent skin testing, two with positive results. Four patients (36%) experienced only mild cutaneous BTRs during their first RDD cycle, and no severe events occurred. The overall BTR rate per cycle was 9.3%. Extending premedication to more than 24 hours before desensitization reduced BTR frequency from 17% to 4%.

Conclusion: RDD proved to be a safe and effective approach for managing HSRs to both common and less frequently used biologic agents. All patients completed treatment without discontinuation. Extended premedication period, multidisciplinary planning, and intensive care unit-based monitoring appear to enhance procedural safety and support the broader implementation of RDD in clinical allergy practice.

Plain Language Summary: Biologic drugs are important treatments for many immune, blood, and cancer-related diseases. However, some patients develop allergic or hypersensitivity reactions that prevent them from continuing these medicines. RDD is a medical procedure that allows patients to safely receive a medication that previously caused a reaction. It works by gradually introducing small doses of the drug until the body temporarily tolerates it.

In this study, we reviewed the experiences of 11 adult patients who had allergic reactions to biologic agents such as rituximab, brentuximab vedotin, daratumumab, and pertuzumab. A total of 43 desensitization cycles were performed under close medical and nursing supervision in an intensive care unit. The desensitization plans were designed together by allergists and clinical pharmacists.

The results showed that the procedure was safe and effective. Mild reactions occurred in a few cases, but no serious problems were seen. When premedication (such as steroids and antihistamines) was started more than 24 hours before the procedure, allergic symptoms were less frequent. This highlights the importance of careful planning and teamwork in making desensitization safer for patients.

Keywords: biological agents, desensitization, drug hypersensitivity, monoclonal antibodies, rapid drug desensitization

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Introduction

Biological agents have revolutionized the treatment of hematologic, rheumatologic, and oncologic diseases, becoming indispensable components of modern clinical practice.[1] However, their expanding use has been accompanied by an increasing incidence of hypersensitivity reactions (HSRs) in recent years.[2] These reactions may lead to substantial morbidity and, on rare occasions, mortality. HSRs are generally categorized as immediate or delayed. Immediate-type reactions may develop through several immunological mechanisms, including infusion-related responses, IgE-mediated pathways, and cytokine release syndrome.[3]

For patients who experience HSRs, rapid drug desensitization (RDD) is a well-established approach that allows the safe continuation of essential treatment by inducing a temporary state of tolerance to the offending agent.[4] Protocols for frequently used biologics such as rituximab and infliximab are well standardized, whereas data on agents like daratumumab, brentuximab vedotin, and pertuzumab remain limited, consisting mainly of individual case reports or small case series.[5–7]

Effective implementation of RDD requires a multidisciplinary approach encompassing patient selection, drug preparation, and administration. The team typically includes an allergist-immunologist, a clinical pharmacist, and an experienced nurse. The allergist evaluates the patient's reaction history, develops the desensitization protocol, and leads the management of breakthrough reactions (BTRs). The clinical pharmacist supervises the preparation phase, ensuring stability of the drug, accurate dilutions, and infusion rates. The nurse plays a central role during administration, preparing emergency equipment, delivering the infusion according to protocol, continuously monitoring for early signs of reaction, initiating the first response if needed, and recording all observations. Continuous communication among team members is critical to maintaining safety throughout the procedure.[8]

The fundamental principle of RDD involves administering the target drug in gradually increasing concentrations at fixed time intervals. In a standard protocol, the drug is infused stepwise from three consecutively prepared solutions with 1:100, 1:10, and 1:1 dilution. The dose is typically doubled at each step, and the entire process is completed in 12 to 16 incremental stages. If a reaction develops during infusion, the procedure is paused, and symptomatic treatment is initiated immediately. Following the resolution of symptoms, the infusion is resumed at the previously tolerated rate.[9]

The immunological basis of the temporary tolerance achieved through desensitization is attributed to the functional anergy of mast cells and basophils. Sequential exposure to gradually increasing doses results in internalization of receptor complexes, inhibition of calcium signaling, and decreased release of mediators such as histamine, tryptase, and prostaglandins. Together, these mechanisms elevate the activation threshold of effector cells upon antigen exposure, thereby preventing a hypersensitivity response. This tolerance, however, is transient and requires repetition of the desensitization procedure before each subsequent drug administration.[10]

In this study, we aimed to evaluate the safety and efficacy of RDD in managing HSRs to rituximab, daratumumab, brentuximab vedotin, and pertuzumab, based on the experience of our tertiary referral center.

Material and Methods

Study Population and Ethical Approval

This study included 11 patients who underwent RDD for HSRs to biological agents at the Department of Allergy and Immunology, Ege University Faculty of Medicine, between 2020 and 2024. The study was approved by the Ethics Committee of Ege University Faculty of Medicine. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Clinical Assessment, Data Collection, and Exclusion Criteria

HSRs were graded based on their severity using Brown's classification: Grade 1 (mild), Grade 2 (moderate), and Grade 3 (severe), following the principles of the Brigham and Women's Hospital protocol.[11] Clinical manifestations were classified by the primary organ system affected, including cutaneous (flushing, pruritus, urticaria, angioedema), cardiovascular (chest pain, tachycardia, hypotension), respiratory (dyspnea, wheezing, hypoxia), gastrointestinal (nausea,

vomiting), and atypical symptoms (fever, chills, back pain). A fever above 38°C was considered a feature of a moderate-grade reaction.

For each patient included, demographic, clinical, and laboratory data were retrospectively collected from electronic health records. This information comprised age, sex, underlying diagnosis, the culprit biological agent, skin test results, serum tryptase, and total Immunoglobulin E (IgE) levels, HSR characteristics (type and grade), premedication regimen, RDD protocol details, and characteristics and management of BTRs. Patients were excluded if their records contained incomplete data or if the reaction was suspected to be due to an alternative cause, such as a co-occurring infection or an infusion-related error.

Skin Testing

Skin testing with the culprit drug was performed in eligible patients for at least six weeks, and no later than six months, after the initial HSR. The procedure began with a skin prick test (SPT); if the result was negative, intradermal testing (IDT) was subsequently performed. All test solutions were aseptically prepared and diluted using a closed robotic system in accordance with established laboratory standards.

Skin testing was performed with drug-specific concentrations, as summarized in Table 1, using available data from previous reports when applicable.[9,12]

Histamine (10 mg/mL) and phenolated glycerol saline served as positive and negative controls, respectively. The result was considered positive when the wheal diameter measured at least 3 mm greater than that of the negative control 20 minutes after application.[13] A positive skin test confirmed an IgE-mediated mechanism, aiding in risk stratification, but did not alter the standard desensitization protocol structure.

Premedication and Desensitization Protocol

All RDD protocols were developed in collaboration with a clinical pharmacist. Each patient received an individualized premedication regimen tailored to the severity of the prior HSR. In patients with a history of severe reactions, oral premedication was initiated 72 hours before the procedure, whereas for those with mild or moderate reactions, it began 24 hours in advance. The standard regimen included methylprednisolone (0.5–1 mg/kg/day), ketotifen (2 mg/day, extended-release), famotidine (40 mg/day), and montelukast (10 mg/day). Aspirin was withheld in most patients due to the increased risk of thrombocytopenia related to their underlying hematologic malignancies.[14] For individuals receiving beta-blocker therapy, treatment was discontinued 24 hours before desensitization following consultation with the prescribing physician.[15]

One hour before desensitization, all patients received intravenous pheniramine (45.5 mg), dexamethasone (20 mg), and ondansetron (8 mg). If a BTR occurred during infusion, the procedure was stopped immediately. Management included supportive measures such as oxygen and isotonic fluid administration, and when necessary, intramuscular epinephrine (0.5 mg), intravenous pheniramine (45.5 mg), cetirizine (10 mg), and methylprednisolone (40 mg). Following clinical stabilization, the infusion was resumed either at the previous step (step-back) or repeated at the same step, depending on the severity of the reaction and the attending physician's judgment. This dynamic adjustment of

Table 1 Concentrations of Biologic Agents Used for Skin Prick and Intradermal Testing

Drug Name	Drug Concentration (mg/mL)	Dilution for Prick Test (mg/mL)	Dilution for Intradermal Test (mg/mL)
Rituximab (n=5)	10	10	0.1 - 1 - 3
Daratumumab (n=3)	20	20	0.2–2
Brentuximab vedotin (n=2)	5	5	0.05–0.5
Pertuzumab (n=1)	30	1.6	0.0016–0.016

Note: Dilutions were prepared in sterile saline according to ENDA/EAACI drug allergy testing recommendations.
Abbreviation: mg/mL, milligram per milliliter.

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infusion rates allowed for the safe completion of the total target dose. Additional premedication doses were administered before restarting if deemed necessary.

Regardless of the skin test result (IgE vs non-IgE mediated), the standard 3-bag, 12-step protocol is recommended as the safest approach for immediate hypersensitivity reactions.[9] Therefore, skin testing was utilized primarily for diagnostic confirmation and risk stratification. The standard 12-step protocol was applied to all patients with Grade 1–2 reactions, while the 16-step protocol was reserved for the single high-risk patient with Grade 3 anaphylaxis, in accordance with established safety guidelines. All desensitization procedures were performed in an intensive care unit with 15-minute intervals between steps, under continuous monitoring and one-to-one supervision by an experienced nurse and attending physician.[16] Strict adherence to this specific time interval is essential to maintain the drug concentration below the threshold of mast cell activation. Prolonged interruptions (typically >30 minutes) were strictly avoided, as gaps in drug delivery can lead to the loss of temporary tolerance (resensitization), potentially triggering a hypersensitivity reaction upon resumption.

Statistical Analysis

All statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize the data. Continuous variables were presented as mean ± standard deviation or median (minimum–maximum) based on their distribution. Categorical variables were reported as frequencies (n) and percentages (%). Due to the descriptive nature of the study and the small sample size, no formal comparative statistical tests were performed.

Results

Patient Characteristics and Clinical Data

A total of 11 patients (8 female, 3 male) who experienced HSRs related to biological agents were included in the study. The demographic, clinical, and procedural characteristics of the study cohort are summarized in Table 2. The mean age was 50 years (range: 21–75). The underlying diagnoses included Hodgkin's lymphoma (n=3), multiple myeloma (n=2), vasculitis (n=2), breast cancer (n=1), rheumatoid arthritis (n=1), Castleman disease (n=1), and AL amyloidosis (n=1).

Table 2 Demographic and Clinical Characteristics of Patients

Case Number	Diagnosis	Age	Gender	Drug	Cycle no of Initial HSR	Grade of the Initial HSR	Systemic Involvement	Skin Test (Prick/ ID)	Number of RDDs Applied	BTRs
1	mPAN	65	F	RTX	2	2	CU, *RS*	N.A.	5	None
2	HL	39	F	RTX	1	2	RS, CVS	N.A.	1	None
3	Castleman disease	37	F	RTX	6	2	CU, *RS*	Negative	4	12th step of 1st RDD: flushing, pruritus
4	V	53	F	RTX	10	2	CU, *RS*	Negative	2	None
5	RA	46	F	RTX	2	1	C	N.A.	6	None
6	MM	60	M	DARA	1	2	RS, GIS	N. A	5	None
7	MM	75	M	DARA	1	1	RS	Negative	1	None
8	AL	59	F	DARA	1	1	RS	Negative	3	None
9	HL	45	M	BV	7	2	CU, *RS*	Positive (ID)	6	11th step of 1st RDD: urticaria
10	HL	21	F	BV	2	3	CU, *RS*, N	N.A.	7	16th step of 1st RDD: flushing
11	Breast Cancer	50	F	PTZ	2	1	CU	Positive (ID)	3	12th step of 1st RDD: urticaria

Abbreviations: AL, AL Amyloidosis; BTRs, breakthrough reactions; BV, Brentuximab vedotin; C, Constitutional; CAST, Castleman disease; CU, Cutaneous; CVS, Cardiovascular system; DARA, Daratumumab; F, Female; GIS, Gastrointestinal system; HL, Hodgkin lymphoma; HSR, Hypersensitive reactions; ID, Intradermal; IgE, Immunoglobulin E; M, Male; MM, Multiple myeloma; mPAN, microscopic polyangiitis; N, Neurological, N.A., Not available; PTZ, Pertuzumab; RA, Rheumatoid arthritis; RDD, Rapid Drug Desensitization, RS, Respiratory system; RTX, Rituximab; V, Vasculitis.

The biological agents responsible for the HSRs were rituximab (n=5), daratumumab (n=3), brentuximab vedotin (n=2), and pertuzumab (n=1).

Laboratory data were available for 5 of the 11 patients. The mean total IgE level was 90.4 kIU/L (range: 0–352), and the mean baseline serum tryptase level was 6.9 ng/mL (range: 1.5–12). Two patients had a history of drug allergy (to trimethoprim/sulfamethoxazole and naproxen sodium, respectively). No other patients reported a history of atopy.

Severity and Clinical Characteristics of the Initial HSRs

According to the severity grading, grade 2 reactions were the most frequent (n = 6), followed by grade 1 (n = 4) and a single grade 3 reaction (n = 1) (Figure 1).

An analysis of the organ systems involved revealed that the respiratory system was the most frequently affected (72%, n=8). This was followed by cutaneous (54%, n=6), gastrointestinal (18%, n=2), and cardiovascular and neurological manifestations (each 9%, n=1).

Skin Testing and RDD Outcomes

Skin testing was performed in six of the eleven patients. Positive results were obtained in two cases—one with pertuzumab and one with brentuximab vedotin. In the remaining five patients, testing could not be completed due to factors such as an inadequate histamine control response, concurrent corticosteroid use, or failure to meet the minimum six-week interval required after the initial reaction.

A total of 43 RDD cycles were conducted across the study cohort. Rituximab was the most frequently administered agent (n=18), followed by brentuximab vedotin (n=13), daratumumab (n=9), and pertuzumab (n=3). The duration of premedication appeared to influence the frequency of BTRs. Among 17 RDD cycles preceded by a 24-hour premedication regimen, three BTRs were observed (17%), whereas only one BTR occurred among 21 cycles in which premedication had been initiated more than 24 hours before the procedure (4%) (Figure 2). In one patient, premedication was administered only immediately before each of the five RDD cycles.

BTRs were observed in four patients during their RDD procedures. Notably, all BTRs occurred during the patients' first RDD cycle, with no subsequent reactions in later cycles. One reaction occurred at step 11 with brentuximab vedotin, while the other three reactions occurred at step 12 with rituximab, pertuzumab, and brentuximab vedotin, respectively. All BTRs were mild and limited to cutaneous symptoms only. No BTRs were observed during any of the RDD cycles involving daratumumab (Table 3).

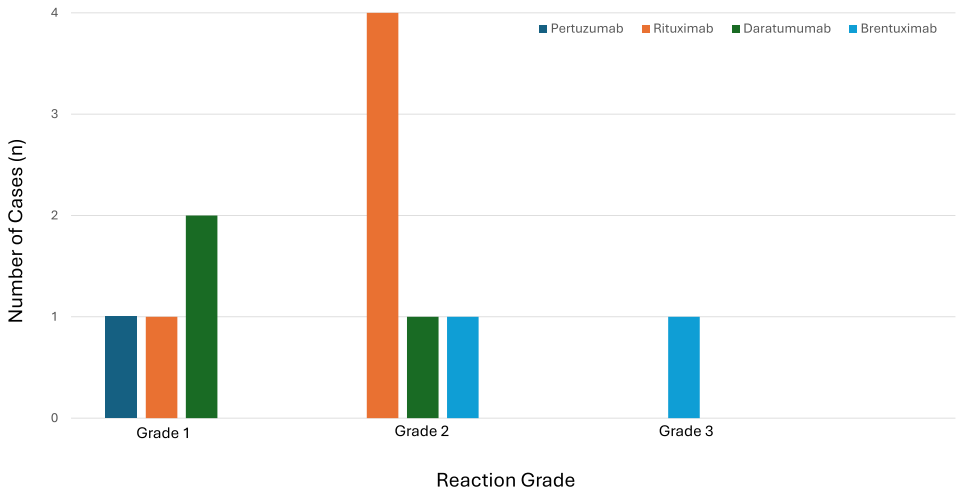

Figure 1 Distribution of HSR severity grades according to the biological agents.

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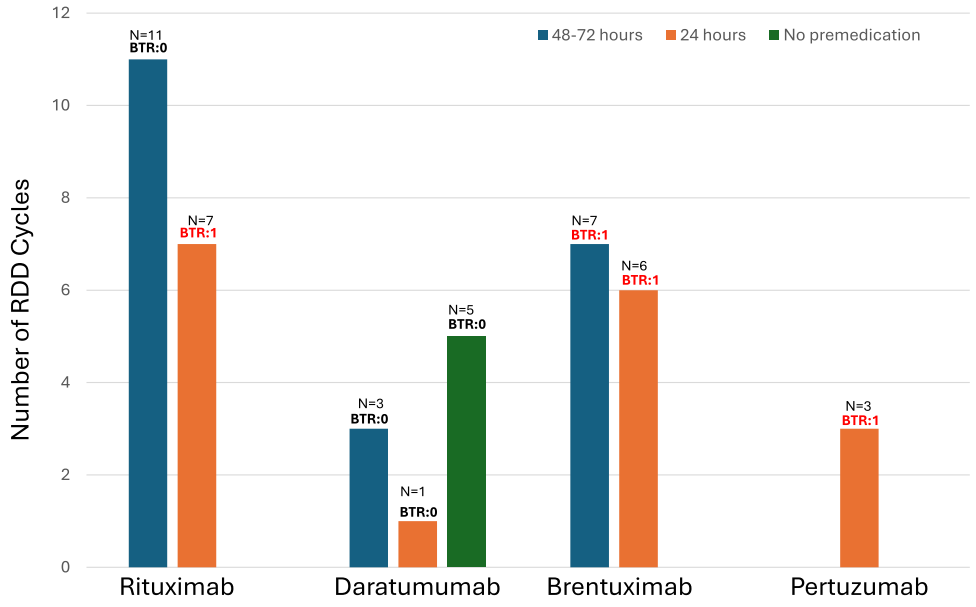

Figure 2 Characteristics of breakthrough reactions during RDD cycles.

Discussion

This study reports our tertiary center's experience, emphasizing the safety and efficacy of RDD in managing HSRs to biologics. Over recent years, RDD has become an integral part of clinical practice, supported by strong evidence demonstrating high success and a favorable safety profile.[2,17,18]

Most studies on RDD have focused on widely used biologics such as rituximab, while data on less common agents—including brentuximab vedotin, pertuzumab, and daratumumab—remain scarce, limited mainly to single case reports or small series.[5,6,9,19]

Rituximab (anti- cluster of differentiation (CD) 20 antibody) is a cornerstone therapy for lymphoproliferative and autoimmune diseases; however, it remains one of the biologics most frequently associated with HSRs. Consequently, it is also the best-documented agent in RDD literature.[15,20] Approximately 5–10% of rituximab-related reactions are IgE-mediated, whereas cytokine release syndrome, mixed-type reactions, and type IV hypersensitivity account for about 13%, 21%, and 3% of cases, respectively.[21] In a review by Castells et al, two patients developed pruritus and one experienced syncope during rituximab RDD, yet all completed therapy.[22] A 2016 study reported a 28% BTR rate among 22 patients,

Table 3 Characteristics and Management of Breakthrough Reactions Observed During RDDs

Case number	Drug	Basal Tryptase (ng/mL)	Premedication	Premedication Initiation Time Before RDD (hours)	BTR STEP	BTR Grade	BTR Definition	BTR Treatment
3	RTX	N.A.	CS, H1RA, H2RA, M	24	12th	I	Flushing, Pruritus	45.5 mg PM + 40 mg MP
9	BV	1.5	CS, H1RA, H2RA, M	24	11th	I	Urticaria	10 mg Z + 40 mg MP + 10 mg M
10	BV	N.A.	CS, H1RA, H2RA, M	72	16th	I	Flushing	45.5 mg PM + 60 mg MP
11	PTZ	7.96	CS, H1RA, H2RA, AE	48	12th	I	Urticaria	45.5 mg PM + 40 mg MP

Abbreviations: AE, Antiemetic; BTR, Breakthrough reaction; BV, Brentuximab Vedotin; CS, Corticosteroid; H1RA, Histamine-1 Receptor Antagonist; H2RA, Histamine-2 Receptor Antagonist; M, Montelukast; mL, milliliter; MP, Methylprednisolone; ng, nanogram; PM, Pheniramine maleate; PTZ, Pertuzumab; RTX, Rituximab; Z, Cetirizine.

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while another involving 29 patients and 176 RDD cycles found a 17% rate, with four patients discontinuing treatment due to grade 3 anaphylaxis.[17,18]

In our cohort, rituximab was responsible for HSRs in 45% of patients (n=5), across a total of 18 RDD cycles. Only one mild BTR (5.5%) occurred, limited to cutaneous symptoms, and it was managed successfully, allowing the treatment to be completed. Although premedication regimens are well standardized, evidence regarding the optimal timing of their initiation remains limited.[9,14,19] The notably lower BTR rate in our series compared with previous reports may reflect the efficacy of our premedication protocol and the relatively mild nature of the initial hypersensitivity reactions (predominantly Grade 1–2) in our cohort. Additionally, sampling variability due to the small cohort size could be a contributing factor to the observed low reaction frequency.

Daratumumab is a human immunoglobulin G1 kappa monoclonal antibody directed against CD 38 and is widely used in the management of multiple myeloma.[23] Most daratumumab-related HSRs arise during the initial infusion, and severe infusion-related reactions have been reported in approximately 3.8% of patients.[24] The high expression of CD38 on respiratory epithelial cells explains why these reactions often manifest with upper respiratory symptoms such as nasal congestion, cough, or dyspnea. Skin tests are generally negative, indicating that non-IgE-mediated mechanisms predominate.[12]

In our series, all patients who reacted to daratumumab exhibited respiratory symptoms, and skin test results were uniformly negative. No BTRs occurred in any RDD cycles, supporting both the safety and effectiveness of our approach. The extended premedication period (≥48–72 hours before desensitization) and meticulous adjustment of infusion rates may have contributed to this outcome. Although most published data involve single cases, our findings represent one of the largest reported series and further support the feasibility of RDD for daratumumab-induced HSRs.[12,25]

Brentuximab vedotin is a monoclonal antibody directed against CD30 and is primarily used in the treatment of refractory Hodgkin's lymphoma and anaplastic large-cell lymphoma.[26] The reported incidence of HSRs associated with this agent is around 13%, with approximately 1.2% classified as grade 3 in severity.[27] In published reports, most HSRs have presented as anaphylaxis, while isolated cases of urticaria have been described; notably, all patients were able to complete subsequent RDDs without major complications.[5,28–31]

In the present series, two patients developed HSRs to brentuximab vedotin—one grade 2 and one grade 3. The patient with a positive intradermal test experienced urticaria at step 11 of the 12-step RDD protocol, and the other developed flushing at step 16 of the 16-step RDD protocol. Both reactions were mild and managed successfully, allowing completion of desensitization. The literature on RDD with brentuximab vedotin often lacks detailed procedural descriptions or information on BTR characteristics. Our findings contribute to this gap by showing that BTRs were limited to mild cutaneous manifestations, supporting the safety and efficacy of RDD in these cases. Furthermore, the successful outcome in a patient with a positive skin test underlines that RDD remains a feasible and safe option for brentuximab-induced HSRs when IgE-mediated mechanisms are suspected.

Pertuzumab is a monoclonal antibody targeting the human epidermal growth factor receptor 2 and is used in the treatment of breast cancer.[32] Most reported HSRs to pertuzumab occur after the first infusion, and the underlying mechanisms likely involve both IgE-mediated hypersensitivity and cytokine release syndrome.[6,7] In our case, the patient with a pertuzumab-induced HSR had a positive skin test and developed urticaria during the first RDD, supporting an IgE-mediated mechanism. The infusion was interrupted, appropriate treatment was given, and desensitization was resumed from the last tolerated step. The procedure was completed without further problems, and subsequent RDD cycles were uneventful. This experience adds meaningful clinical data to the limited literature on RDD for pertuzumab-related HSRs.

Although systematic biomarker data (eg, tryptase, cytokines) were limited, we evaluated the clinical phenotypes of the reactions based on the timing of the initial HSR, skin test results, and BTR characteristics, as summarized in Table 4.

Rituximab-induced HSRs in our cohort exhibited a heterogeneous profile. Cases 1, 2, and 5 experienced reactions during the first or second infusion, consistent with non-IgE mediated Cytokine Release Syndrome (CRS) or infusion-related reactions (IRR) commonly reported in the literature.[21] In contrast, Cases 3 and 4 developed reactions after multiple exposures (6th and 10th cycles), suggesting a potential sensitization process; however, negative skin tests and non-cutaneous BTRs (eg, flushing) in these patients point towards a mixed or non-IgE mechanism rather than a pure Type I allergy.

Regarding daratumumab, all three patients reacted during the first infusion with predominantly respiratory symptoms, and skin tests were negative. This clinical presentation strongly aligns with the non-IgE mediated IRR phenotype, likely

Table 4 Proposed Clinical Phenotypes of Hypersensitivity Reactions to Biological Agents

Biological Agent	Case No	Initial HSR Timing (Infusion cycle)	Skin Test Results	BTR Characteristics	Proposed Clinical Phenotype
Rituximab	1, 2, 5	1st, 2nd	N. A	None	Non-IgE (CRS/IRR)
Rituximab	3, 4	6th, 10th	Negative	Flushing, pruritus	Mixed/non-IgE
Daratumumab	6, 7, 8	1st	Negative (n=2)	None	Non-IgE (CRS/IRR)
Brentuximab Vedotin	9	7th	Positive (ID)	Urticaria	IgE-mediated
Brentuximab Vedotin	10	2nd	N.A.	Flushing	Mixed/non-IgE
Pertuzumab	11	2nd	Positive (ID)	Urticaria	IgE-mediated

Abbreviations: CRS, Cytokine Release Syndrome; IRR, Infusion-Related Reaction; ID, Intradermal; N.A., Not Available.

driven by CD38 expression on airway epithelium, as described in previous articles.[12,24] The absence of BTRs in these patients further supports a mechanism distinct from high-affinity IgE-mediated anaphylaxis.

Conversely, reactions to brentuximab vedotin and pertuzumab showed features suggestive of an IgE-mediated mechanism. Specifically, case 9 (brentuximab) and case 11 (pertuzumab) had positive intradermal tests and manifested breakthrough urticaria during desensitization. These findings are consistent with rare but documented IgE-mediated allergies to these agents, typically requiring a period of sensitization.[7,29]

Beyond drug-specific outcomes, our findings also highlight procedural factors that may influence RDD safety. The BTR rate was 17% in cycles preceded by a 24-hour premedication regimen, whereas it dropped to 4% when premedication was initiated more than 24 hours before the procedure. This finding is noteworthy; however, due to the limited number of cases, formal statistical analysis could not be carried out. Therefore, this observation requires further evaluation in future large-scale cohort studies. The observed clinical trend suggests that extending the premedication period beyond one day may potentially improve the safety of desensitization. Prolonged corticosteroid and antihistamine administration likely contributes by providing stronger mast cell stabilization and greater suppression of cytokine release.[33]

This study has several limitations. First, its single-center, retrospective design restricts the generalizability of the results. Second, the relatively small sample size—especially for the less frequently used biologics—limits the statistical strength of our conclusions. Finally, variations in premedication protocols and the use of non-validated skin test concentrations for certain agents may have influenced both the classification and outcomes of HSRs. In addition, the lack of systematic biomarker data (eg, serum tryptase, cytokine profiles) prevented a definitive molecular endotypic classification; therefore, phenotypic evaluation was restricted to clinical features and skin test results.

Conclusion

Our study demonstrates that RDD is a safe and effective approach for managing HSRs to both commonly and less frequently used biologic agents, enabling patients to continue their essential first-line therapies. Across 43 RDD cycles, all participants successfully received their full target doses. The overall BTR rate was low (9.3%), and all reactions were mild and limited to cutaneous manifestations. A longer premedication period (>24 hours) was associated with a lower frequency of BTRs compared with the standard 24-hour regimen. When performed by an experienced multidisciplinary team, RDD remains an indispensable procedure for patients with HSRs who lack alternative treatment options.

AI Assistance Statement

Sections of this manuscript (including language editing and formatting) were assisted by ChatGPT (OpenAI, version GPT-5) under the supervision of the corresponding author. The tool was used to improve English clarity and formatting; all content was reviewed and verified by the authors.

Abbreviations

AE, antiemetic; AL, amyloidosis; BTR, breakthrough reaction; BV, brentuximab vedotin; CAST, Castleman disease; CD, cluster of differentiation; CS, corticosteroid; CU, cutaneous; CRS, cytokine Release Syndrome; CVS, cardiovascular system; DARA,

daratumumab; EAACI, European Academy of Allergy and Clinical Immunology; ENDA, European Network on Drug Allergy; F, female; GIS, gastrointestinal system; HL, Hodgkin lymphoma; H1RA, histamine-1 receptor antagonist; H2RA, histamine-2 receptor antagonist; HSR, hypersensitivity reaction; ICU, intensive care unit; ID, intradermal; IDT, intradermal test; IgE, immunoglobulin E; IRR, infusion-related reactions; kIU/L, kilo–international units per liter; M, male; mg, milligram; mg/kg, milligram per kilogram; mg/mL, milligram per milliliter; mL, milliliter; MM, multiple myeloma; MP, methylprednisolone; mPAN, microscopic polyangiitis; N, neurological; N.A., not available; PM, pheniramine maleate; PTZ, pertuzumab; RA, rheumatoid arthritis; RDD, rapid drug desensitization; RS, respiratory system; RTX, rituximab; SD, standard deviation; SEM, standard error of mean; SPSS, Statistical Package for the Social Sciences; SPT, skin prick test; Z, cetirizine.

Data Sharing Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

The study was approved by the Ethics Committee of Ege University Faculty of Medicine (approval number: 25-3.1T/32). Written informed consent was obtained from all participants before inclusion in the study. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Consent for Publication

Consent for publication was obtained from all participants included in the study.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflict of interest.

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