ORIGINAL ARTICLE

Adrenaline: A Lifeline for Rapid Drug Desensitization in Hypersensitive Patients

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Abstract

Background: Chemotherapeutic agents (CMTs) and monoclonal antibodies (mAbs) are common causes of drug allergy, which is often managed using rapid drug desensitization (RDD). Despite its effectiveness, RDD can be hampered by severe breakthrough reactions (BTRs), potentially leading to failure of the procedure.
Objective: To evaluate the usefulness and safety of adrenaline infusion (AI) as an adjuvant during RDD in patients who experience severe drug hypersensitivity reaction (DHR) during standard desensitization protocols.
Methods: Retrospective observational study, analyzing data from patients who underwent RDD to CMTs or mAbs in a tertiary hospital from January 2015 to June 2024. We included patients who required AI to safely achieve RDD after a severe initial DHR or failure of a standard RDD protocol due to repeated DHRs. Comorbidities, adrenaline doses, and adverse events (AEs) were assessed.
Results: RDD with AI was administered in 42 patients. Of these, 77% (n=32) were women, and the mean age was 57 years. The most frequently involved drugs were platinum salts (58%), mAbs (26%), and taxanes (14%). A total of 151 RDDs were performed with AI. Skin tests were positive in 69% of patients. The most frequent initial BTR (65%) was moderate or severe anaphylaxis. The most common AEs induced by AI were tremor (14%) and tachycardia (7%), which resolved after reducing the AI infusion rate. The median (IQR) cumulative dose of adrenaline administered throughout the RDD procedure was 0.76 mg (0.4-1.2mg), with a median infusion rate of 8 mL/h (4-15ml/h), and median maximum AI rate of 3.33 µg/min (2-5.3 µg/min).
Conclusions: AI is a useful and safe therapeutic tool for selected high-risk desensitization procedures, mitigating severe DHR with mostly minor AEs.

Key words: Adrenaline infusion. Chemotherapy. Drug hypersensitivity reactions. Monoclonal antibodies. Rapid drug desensitization.

Resumen

Antecedentes: La quimioterapia (CMT) y los anticuerpos monoclonales (mAbs) son causas frecuentes de alergia a medicamentos, a menudo tratadas mediante desensibilización rápida a medicamentos (RDD). A pesar de su efectividad, la RDD puede verse dificultada por reacciones de graves (BTR) durante el procedimiento, lo que puede llevar a su fracaso.
Objetivo: Evaluar la utilidad y seguridad de la infusión de adrenalina (AI) como coadyuvante durante la RDD en pacientes con reacciones de hipersensibilidad a medicamentos (DHR) graves durante los protocolos estándar de desensibilización.
Métodos: Estudio observacional retrospectivo, que analizó datos de pacientes que se sometieron a RDD para CMT o mAbs en un hospital terciario entre enero de 2015 y junio de 2024. Se incluyeron pacientes que precisaron AI para completar la RDD de forma segura tras una DHR grave inicial o el fracaso de los protocolos estándar de RDD debido a reacciones repetidas. Se evaluaron comorbilidades, dosis de adrenalina y eventos adversos (AE).
Resultados: La RDD con infusión de adrenalina se realizó en 42 pacientes. El 77% (n=32) eran mujeres con una edad media de 57 años. Los medicamentos más frecuentes fueron sales de platino (58%), mAbs (26%) y taxanos (14%). Se realizaron 151 procedimientos de RDD con AI. Las pruebas cutáneas fueron positivas en el 69% de los pacientes. La BTR inicial más común (65%) fue la anafilaxia moderada o grave. Los AEs comunes de la AI fueron temblores (14%) y taquicardia (7%), que se resolvieron al reducir la tasa de infusión de AI. La dosis acumulada media de adrenalina administrada fue 0,76 mg (IQR 0,4-1,2 mg), con una tasa media de infusión de 8 ml/h (IQR 4-15 ml/h) y una tasa máxima de AI de 3,33 µg/min (IQR 2-5,3 µg/min).
Conclusiones: La AI es una herramienta terapéutica útil y segura para procedimientos de desensibilización de alto riesgo seleccionados, reduciendo reacciones graves con AEs leves.

Palabras clave: Infusión de adrenalina. Quimioterapia. Reacciones de hipersensibilidad a medicamentos. Anticuerpos monoclonales. Desensibilización.

Summary box

- **What do we know about this topic?**
  Desensitization is a useful tool for managing hypersensitivity reactions to chemotherapeutic agents and monoclonal antibodies. However, while the failure rate of the procedure is low, there are instances where desensitization cannot be completed owing to multiple/severe breakthrough reactions (BTRs).
- **How does this study impact our current understanding and/or clinical management of this topic?**
  The adrenaline infusion is a useful, safe, inexpensive, and feasible adjuvant treatment in rapid drug desensitization, particularly for high-risk patients and those who experience BTRs that may require discontinuation of the procedure.

Introduction

Anaphylaxis is the most severe clinical presentation of acute systemic allergic reactions. Its onset is rapid, and it can be fatal [1,2]. The worldwide incidence of anaphylaxis ranges from 50 to 112 episodes per 100 000 person-years, and the prevalence is 0.3% to 5.1% [1-5]. Chemotherapeutic agents (CMTs) and biological drugs, particularly monoclonal antibodies (mAbs), are common causes of drug hypersensitivity reactions (DHRs), which occur in approximately 3% to 5% of administrations [2,3,6]. Platinum salts and taxanes are frequent culprits among CMTs, while most mAbs have been reported to be able to trigger DHRs [3-8]. Immediate DHRs (<1 hour) to CMT/mAbs are classified according phenotype as mast cell/basophil–mediated, cytokine-mediated (or cytokine release), and mixed (ie, a combination of the first 2 types) [3,4,6,9-11].

Desensitization is the primary therapeutic option for patients who have experienced DHRs to essential medications. This procedure modifies the immune allergic response, fostering temporary tolerance [3,6,12]. Single-bag rapid drug desensitization (RDD) protocols have proven to be effective strategies [8,13,14]. Despite its established safety, desensitization fails in a small proportion of patients (less than 10%) owing to breakthrough reactions (BTRs) during the procedure [7,10,13-16]. However, a subset of patients cannot tolerate this procedure because of repeated or severe BTRs.

The first-line treatment for anaphylaxis is intramuscular adrenaline (injected into the quadriceps). In patients with refractory anaphylaxis, the intravenous route can be used with diluted adrenaline under strict monitoring by experienced personnel [1,2,17-20]. There are no absolute contraindications for the use of adrenaline in anaphylaxis. Adrenaline can cause adverse effects such as tachycardia, distal tremor, and headache, as well as cardiovascular complications especially, if undiluted intravenous adrenaline is administered [18]. Nevertheless, adrenaline is effective in preventing and reversing bronchospasm and cardiovascular collapse during anaphylaxis. In addition, onset is rapid, half-life is short, and survival rates have improved [1,2,17,19,21-25].

In 2012, we started to administer intravenous adrenaline during high-risk desensitization protocols for patients experiencing recurrent BTRs. Following its successful implementation and favorable tolerance, this method was adopted more frequently in subsequent cases with the new protocol, which started in 2015. The aim of the present study was to describe the use of an individually titrated adrenaline infusion (AI) as adjunctive therapy during standard desensitization procedures for CMT/mAbs in patients who have experienced life-threatening DHRs or moderate-to-severe BTRs that jeopardize continuation of treatment.

Methods

A retrospective, observational study was conducted to analyze data from desensitization procedures performed at the tertiary institution Hospital Universitari Vall d'Hebron in Barcelona, Spain. We included patients from January 2015 to June 2024 who underwent desensitization to CMTs or mAbs and who required the use of AI to safely achieve RDD after failure of the standard RDD protocol (both at our and other centers). The study was approved by the Ethics Committee of University Hospital Vall d'Hebron (project code EOM[AG]003/2023[6083]). Informed consent for the desensitization procedure was obtained from all participants.

Study Population

Inclusion criteria

The study population comprised high-risk adult patients (age ≥18 years) who fulfilled 1 of the following criteria:

- Extreme immediate DHR (cardiac arrest, anaphylactic shock, or mixed DHR grade 4-5 according to the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] [26] and/or grade 3 of the Brown classification [27]) during the infusion of any CMT/mAbs requiring adrenaline.
- Moderate-severe DHRs during RDD [25,26] and need for several doses of intramuscular adrenaline to complete the desensitization protocol.
- Positive skin test result to the culprit drug and an acute serum tryptase increase of (120%+2) in basal serum tryptase during the DHR.
- Failure of desensitization at another hospital.

Exclusion criteria

- Not signing the informed consent.
- Successful completion of the RDD protocol with no BTRs or only mild reactions that do not prevent the RDD from being completed.
- Delayed DHR.

Allergy Assessment and Desensitization Procedures

Patients with suspected immediate DHR underwent an allergy assessment involving a comprehensive clinical history for risk stratification, along with skin tests with the culprit drug. Initial reactions were graded according to the criteria of the NCI-CTCAE [26] and the Brown classification [27].

Skin tests were performed with nonirritating dilutions, as previously described [28]. RDD was performed following our published 1-dilution protocol [8]. A positive skin test result was defined as a wheal diameter >6 mm or greater than the positive control test wheal.

Premedication was tailored based on patients' previous reactions and our allergy desensitization protocol, in addition to the premedication recommended by the CMT manufacturer. However, most patients received systemic 6-methylprednisolone at doses of 1 mg/kg and intravenous dexchlorpheniramine 5 mg before starting the RDD. Home premedication was not prescribed, and ß-blockers and angiotensin-converting enzyme inhibitors were not discontinued.

We decided to perform the 1-bag RDD protocol instead of a 3- to 4-bag protocol, since this approach has proven robust, effective, and useful for managing DHR [8,13,14,29-33]. In addition, its safety and efficacy profile is comparable to that of multibag protocols. From a cost-effectiveness perspective, 1-bag protocols simplify preparation and administration of the drug, reducing resource utilization in terms of pharmacy workload, nursing, and materials and minimizing the potential errors associated with bag switching. We highlight that, currently, the characteristics of high-precision pumps enable precise infusion rates at very low doses. The number of steps and drug administration rate in our 1-bag protocol was the same as that used in the 3- to 4-bag protocol. We primed the infusion system with the drug to ensure accurate control of the dose administered from initiation and added saline serum or glucose 5% solution (according to the manufacturer's instructions) through a Y port at 200 mL/h to ensure the infusion of the CMT or mAb.

Besides, with the use of high-precision infusion pumps, the 1-bag method enables precise dose control and real-time adjustments to infusion rates, ensuring patient safety during desensitization. In our experience, since adding steps to the RDD does not prevent BTRs, we have explored other strategies, such as titrated AI, which we applied as an adjunctive therapy during desensitization in high-risk patients. Moreover, the 1-bag protocol saves valuable time, enabling faster initiation and completion of treatment, which is important in high-risk patients such as those of our study cohort.

Rapid Drug Desensitization Protocol

We performed the RDD following our previously described protocol [8]. Step durations (ranging from 15 to 20 minutes) were individualized based on the patient's prior reactions and skin test results. For some patients with significantly positive skin test results or those who experienced moderate-to-severe reactions at the onset of desensitization, a longer protocol with 20-minute steps and a single-bag infusion was used.

Adrenaline Infusion

RDD was performed with the support of AI. We used a solution of 1 mg of adrenaline in 50 mL of saline solution (20 µg/mL) and performed individualized titration based on patients' tolerance, with infusion rates not exceeding 0.1 µg/kg/min according to literature safety assessments and guideline recommendations [17,19,20,24,34-36]. The infusion rate was adjusted according to blood pressure and heart rate (not exceeding 20% of the baseline value) and/or symptoms

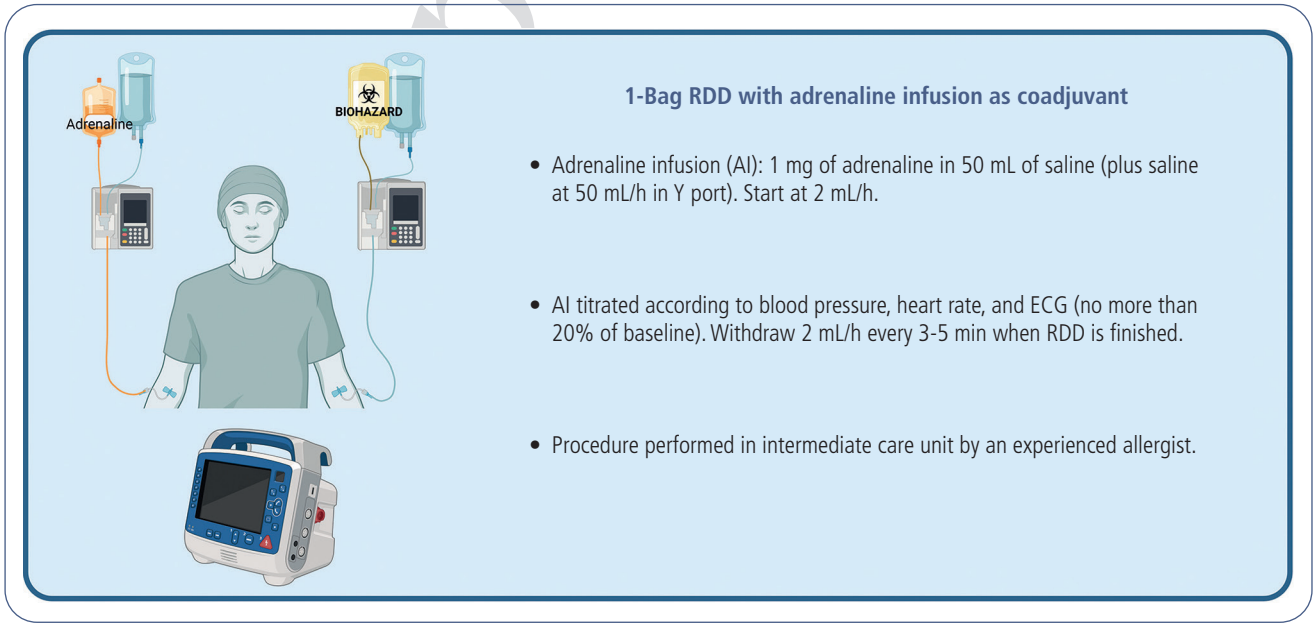

Figure 1. Visual summary of the technical aspects of the adrenaline infusion during RDD. AI indicates adrenaline infusion; RDD, rapid drug desensitization. Created in BioRender. Gil-Serrano, J. (2024) BioRender.com/l60l400.

such as tremor, headache, palpitations, and chest pain. Saline solution was administered concurrently through a Y port at a rate of 50 L/h during the procedure. All procedures were carried out in the intermediate care unit under strict monitoring of blood pressure, ECG, and oxygen saturation (Figure 1).

Biomarkers

Serum tryptase was measured using the UniCAP-Tryptase fluoroimmunoassay (Phadia, now Thermo Fisher Scientific), according to the manufacturer's instructions. The normal range for serum tryptase is 0-11.4 μg/L. An elevation in tryptase during the reaction was considered significant if acute serum tryptase increased (120%+2) above baseline levels.

Serum IL-6 was determined following the routine hospital laboratory protocol, with a normal range of 0-4.3 pg/mL. Elevated values were arbitrarily defined as an increase of more than 50% over baseline during the reaction and above the measurement range of detection.

Statistical Analysis

We performed a retrospective analysis of an electronic database of patients with immediate DHRs to CMT/mAbs from January 2015 to June 2024, including demographic data, comorbidities, culprit drug, skin tests, number of chemotherapy cycles received prior to the immediate DHRs, tryptase and IL-6 levels during the reactions and at baseline, and number of desensitization protocols required with AI. We evaluated the median cumulative dose of adrenaline, median infusion rate, and safety of drug use/adverse events (AEs). Data were entered into a Microsoft Excel database and analyzed using IBM SPSS Statistics for Windows, Version 19.0 (IBM Corp). A descriptive analysis of the frequencies of the variables was made. Continuous variables and their default are expressed as mean and median with their 95%CI; qualitative variables are expressed as absolute numbers and percentages.

Results

Patients' Characteristics

During the study period, 1396 RDD procedures were performed on 538 patients, with 7.8% (n=42) of the patients fulfilling the inclusion criteria for the use of AI. Among these, 77% (n=32) were women, and the mean age was 57 years (range, 32-83). Regarding underlying disease, 45% (n=19) were being treated for gynecological cancer, 7% (n=3) for breast cancer, 19% (n=8) for gastrointestinal cancer, 7% (n=3) for multiple sclerosis, 11% (n=5) for other autoimmune diseases, 5% (n=2) for hematological malignancies, 2% (n=1) for laryngeal cancer, and 2% (n=1) for endocrinological cancer. Patient number 17 had 2 different reactions to 2 anti-CD20 monoclonal antibodies (rituximab and ofatumumab) requiring the use of AI in both to achieve RDD.

Three patients were receiving β-blocker treatment and 3 were receiving angiotensin-converting enzyme inhibitors.

Seventy-nine percent of patients (n=33) had undergone more than 1 treatment course prior to experiencing the initial reaction, suggesting prior sensitization to the drug. Among these 33 patients, 31 had their initial reaction after 3 or more administrations. Two patients, who had not previously received treatment, experienced their reaction after several cycles (seventh and eighth, respectively), of platinum-based drugs in both cases. Seven patients experienced their initial reaction during the first administration of the drug (2 with paclitaxel, 3 with rituximab, 1 with ofatumumab, 1 with cetuximab), with no previous treatment courses or cycles. The patient who reacted to cetuximab, patient 18, also had sIgE to α-gal; therefore, an IgE-mediated reaction to cetuximab was suspected.

Twenty-one percent of patients (9/42) were referred from other national hospitals owing to the failure of their desensitization protocol. In 7 cases, carboplatin was the culprit drug (4 had undergone a previous 3-bag RDD protocol). One had reacted to oxaliplatin. The last patient experienced a DHR to paclitaxel and underwent an RDD at another hospital. This manifested as anaphylactic shock with severe bronchospasm, leading to discontinuation of the treatment.

Patient characteristics are shown in Supplementary Table I.

Culprit Drug

We found that 58% of cases (n=25) involved platinum-based drugs, as follows: carboplatin in 35% (n=15), oxaliplatin in 21% (n=9), and cisplatin 2.3% (n=1). Taxanes accounted for 14% of cases (n=6), all of which involved paclitaxel. One patient had a reaction to liposomal doxorubicin (2%). mAbs were responsible for 26% of the reactions, the most frequent being with rituximab (n=7), ocrelizumab (n=1), cetuximab (n=1), natalizumab (n=1), and ofatumumab (n=1).

Allergy Workup

Skin tests

Skin tests were performed in all patients, except for the patient who reacted to doxorubicin (owing to its vesicant properties). The results were positive in 69% of patients (n=29: 15 to carboplatin, 9 to oxaliplatin, 1 to cisplatin, 1 to cetuximab, 1 to paclitaxel, 1 to rituximab, and 1 to natalizumab).

Severity and phenotype of reactions

Based on the Brown classification [27], the distribution of reactions was as follows: grade 1, 16.3% (n=7); grade 2, 23.3% (n=10); grade 3, 59.5% (n=25). According to the NCI CTCAE classification [26], no grade 1 reactions were observed, while 32.5% (n=14) were grade 2, 21% (n=9) were grade 3, and 46.5% (n=20) were grade 4, with 1 case resulting in cardiorespiratory arrest.

Upon assessing phenotypes, as previously described [11], we observed 65% of reactions (n=28) to be mast cell-/basophil-mediated, 14% (n=6) to be cytokine-mediated or cytokine release reactions, and 20.9% (n=9) to be mixed reactions.

Serum biomarkers

We assessed tryptase and IL-6 levels during the initial reaction when available. Among the 42 patients, acute tryptase levels were measured during 28 reactions and were significantly elevated in 68% (19/28) of these cases. The mean acute tryptase value was 23 μg/L (range, 9.9-80 μg/L). The

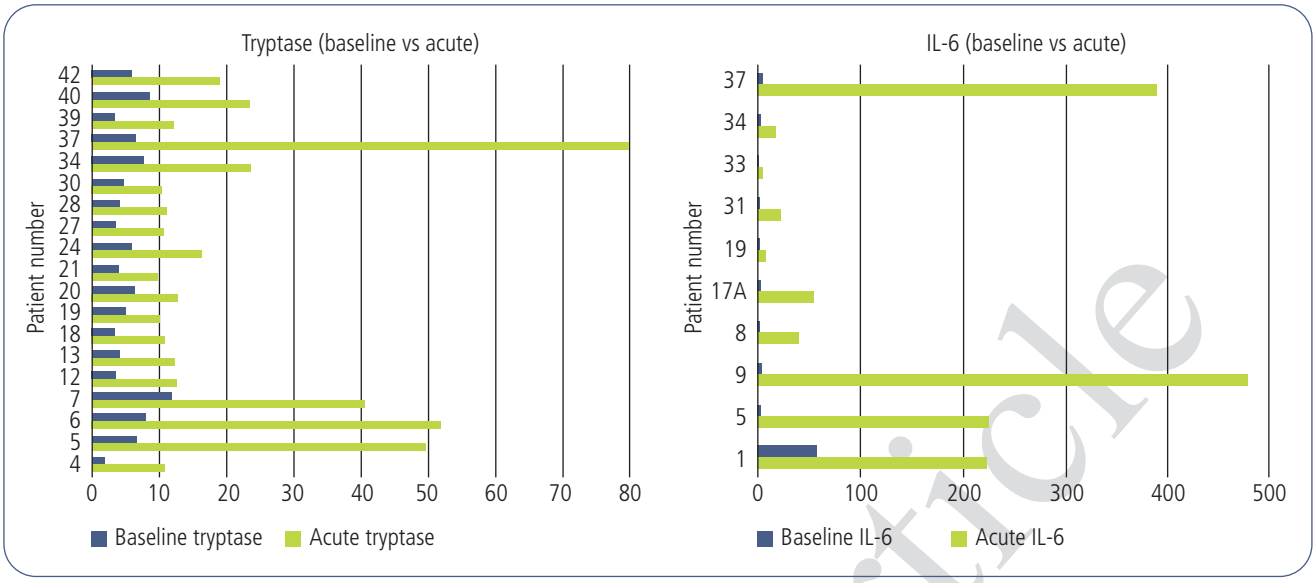

Figure 2. A, Serum tryptase. Acute and baseline serum tryptase values (µg/L) in patients with elevated basal serum tryptase values during the reaction [≥(120%+2)]. B, Serum IL-6. Acute and baseline interleukin 6 (IL-6) values (pg /mL) in patients with elevated values during the reaction. Arbitrarily defined as an increase of more than 50% over baseline levels during the reaction and above the measurement range of detection.

mean baseline tryptase level was 6 µg/L (range, 1.9-12 µg/L). IL-6 levels were measured during the reaction in 11 out of 43 cases, with elevated values observed in 10 patients (median acute value, 147 pg/mL [range, 5.03-480 pg/mL]). The mean baseline IL-6 value was 3.6 pg/mL (range, 1.5-59.4) (Figure 2A and B).

Adrenaline Infusion

A total of 151 RDD protocols were performed with AI in 42 patients. AI was initiated in all patients at a rate of 2 mL/h, and the dose was gradually increased to a rate slightly below that resulting in a 20% increase in heart rate and/or blood pressure. At this point, the RDD protocol was initiated. The median (IQR) cumulative dose of adrenaline administered throughout the procedure was 0.76 mg (0.4-1.2 mg/L [SD, 3.05]), with a median infusion rate of 8 mL/h (4-15 mL/h) and a median maximum AI rate of 3.33 µg/min (2-5.3 µg/min). After completing the RDD, the AI was tapered 2 mL/h every 3-5 minutes until cessation to prevent a sudden decrease in systemic vascular resistance and blood pressure.

Breakthrough Reactions

We managed BTRs during RDD with AI depending on severity. First, we stopped the drug infusion and treated patients according to the severity of the BTR. Mild reactions such as itch, palmar erythema, and urticaria were treated with antihistamines (intravenous dexchlorpheniramine 5 mg); in the case of mild-moderate angioedema, we added intravenous methylprednisolone 40-60 mg. If associated symptoms such as rhinitis, dyspnea, or gastrointestinal symptoms developed, we increased the AI rate slightly (1 mL/h every 3-5 minutes) until improvement. After remission of symptoms, we restarted RDD.

Forty-four percent of the patients did not experience a BTR, and only 1 patient reported anaphylaxis (grade 2 according to the Brown classification) [27]. All patients received the full treatment dose within a timeframe of 3-5 hours. Supplementary Table 1 provides a detailed description of BTR during the desensitization procedure.

Adverse Events

Adrenaline was well tolerated by all patients with 1 exception. The most frequent AE was tremor (n=6), which was alleviated by reducing the infusion rate. Elevated blood pressure was reported in 2 patients, mild tachycardia in 3, isolated ventricular extrasystole in 1, and malaise in 1; all these symptoms were successfully managed by lowering the AI rate. Only 1 (patient 26) decided not to continue with the procedure after completing 2 RDD protocols owing to poor tolerance of mild AEs.

Discussion

Ours is the first study to describe the use of intravenous AI as an adjunct therapy to RDD in DHR to CMTs and mAbs.

Since desensitization is a safe procedure, most patients tolerate the target dose of the drug. In some cases, patients develop reactions during the procedure, although these are usually milder than the initial reaction and are treated immediately. Therefore, it is usually possible to continue and conclude the treatment. However, approximately 10% of patients experience serious or very early reactions during the procedure, hampering completion of treatment, sometimes without optimal therapeutic alternatives [7,10,12-15]. There have been several reports of omalizumab being administered to facilitate high-risk RDD [37-40]. Unfortunately, in 2015, when we started using this protocol, the published evidence on the adjuvant effect of omalizumab in desensitization to CMTs was scarce [38,39]. Even today, established protocols for the

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appropriate dosage and duration of omalizumab in this setting are lacking and remain an area of ongoing investigation. The use of omalizumab as an adjuvant treatment may be a viable strategy to reduce risk in patients with severe IgE-mediated hypersensitivity reactions. However, not all the patients in our study had suspected IgE-mediated hypersensitivity reactions, and omalizumab is not a standard treatment for cytokine release syndrome or mixed reactions, whereas adrenaline is. Therefore, we opted for this alternative. Similarly, the urgent need to initiate RDD for CMTs and mAbs in our study prompted us to search for strategies to improve tolerance. Moreover, AI could prove less expensive than omalizumab and could be an alternative in countries with restricted access to omalizumab. In our cohort, AI proved effective in mitigating mast cell-/basophil-triggered symptoms and ensuring the successful completion of RDD. Additionally, AI proved useful in managing patients with cytokine release reactions and mixed reactions and enabled us to successfully desensitize patients referred from other centers, where previous desensitization protocols had failed. The median cumulative dose of adrenaline administered throughout the RDD procedure was 0.76 mg (0.4-1.2 mg [SD, 3.05]), which is lower than the doses of intramuscular adrenaline that patients had previously received or would have received when the BTR occurred.

We recorded a low rate of AEs to AI. All the AEs were mild. The most frequent was tremor, which was resolved by reducing the infusion rate.

In a canine model, Mink et al [24] compared different routes of adrenaline administration (intramuscular, subcutaneous, and intravenous) during an allergen challenge. The results showed that a constant infusion of low-dose adrenaline was more effective for improving hemodynamic symptoms in dogs than other delivery methods. These results suggest that AI could be a valuable tool for managing similar conditions. Moreover, in a Japanese cohort with severe anaphylaxis refractory to repeated intramuscular adrenaline, a series of 7 patients [41] required AI during oral food challenge, thus demonstrating the usefulness and safety of AI. Fujizuka et al [36] compared intramuscular adrenaline with intravenous infusion and concluded that intravenous adrenaline infusion was safe, effectively alleviates anaphylaxis symptoms, and is associated with fewer AEs. The recent findings of Toledo-Salinas et al [42] for an RDD protocol with methotrexate and AI as an adjuvant further demonstrate the clinical utility of this option.

We show that AI enhances the safety of desensitization by reducing both the frequency and the severity of reactions. It enables prompt management of DHRs, including urticaria, angioedema, bronchospasm, anaphylaxis, and hypotension, using low doses of adrenaline. In our experience, this approach effectively minimizes the risk of severe AEs and facilitates the successful completion of high-risk RDD procedures within fewer hours, including those deemed unsuccessful at other centers.

AI administered via high-precision pumps enables precise dose titration based on individual patient responses, ensuring optimal symptom control while minimizing the risk of AEs.

Limitations

This study has several limitations. It lacks a comparison with a control group owing to the challenges involved in finding patients with comparable comorbidities and sensitization profiles. Consequently, patients' previous reactions were used as internal controls. Additionally, this is a single-center study with a "relatively" small sample size, and our strategy was not compared with other strategies for reducing reactions, such as premedication with omalizumab. Nevertheless, from a practical perspective, adrenaline is a physiological and widely used agent for managing DHR, and the availability and low cost of this strategy make it an affordable and feasible option for many centers around the world.

Conclusions

AI is a valuable therapeutic tool during selected high-risk RDD, aiding in the control of allergic reactions and enhancing the safety of the procedure. Our findings offer novel insights into the efficacy and safety of integrating intravenous adrenaline into RDD protocols. The results underscore the importance of strict monitoring by an experienced allergist to manage potential AEs and contribute valuable data for optimizing desensitization strategies in patients with hypersensitivity reactions to CMTs and mAbs.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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