Desensitization for Hypersensitivity Reactions to Medications

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Abstract

Rapid drug desensitization (RDD) is a technique that induces temporary tolerance to a drug, allowing a medication-allergic patient to receive the optimal agent for his or her disease. Through RDD, patients with IgE and non-IgE hypersensitivity reactions (HSRs) including anaphylaxis can safely be administered important medications while minimizing or completely inhibiting adverse reactions. Adverse reactions to drugs are increasingly recognized as important contributors to disease as well as impediments to the best treatment of dermatological, infectious, autoimmune, and neoplastic disorders. With the development of novel pharmacologic agents and the evolution of personalized treatments based on pharmacogenetic profiling, clinicians must decide which agent is the best for a particular patient with a given disease. Biological agents have greatly improved the treatment of chronic inflammatory diseases and malignancies while limiting some medication-associated toxicities. Because of better outcomes, longer patient survival, and extended treatment courses, patients are exposed to drugs more frequently and for longer time periods, increasing the risk of sensitization and the potential for HSRs. The frequency of adverse drug reactions has therefore increased in the last 10 years. Because of the severity of some reactions and the fear of inducing a potentially lethal reaction in highly sensitized patients, first-line treatments are sometimes abandoned, relegating hypersensitive patients to secondary, less effective, therapy. Some of these reactions are mast cell-mediated HSRs, a subset of which occur through an IgE-dependent mechanism, and are thus true allergies. Others involve mast cells, but an IgE mechanism cannot be demonstrated. Both types of reactions are amenable to RDD, and our group has successfully performed several hundred desensitizations to chemotherapy, antibiotics and biological agents including monoclonal antibodies with a standardized 12-step protocol that can be universally applied to all desensitizations. The molecular basis of RDD has now been studied, and an in vitro mouse mast cell model has shown that RDD is an antigen-specific process that does not induce subclinical mast cell mediator release, and that blocks the release of acute and late mast cell mediators by preventing calcium influx and antigen/IgE and IgE receptor internalization.

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Essentials in a Nutshell

- Rapid desensitizations are safe and effective for the treatment of type I IgE-dependent and IgE-independent hypersensitivity reactions (HSRs), including anaphylaxis
- In vitro rapid drug desensitization (RDD) is an antigen-specific process that does not induce subclinical mast cell mediator release and prevents antigen/IgE/IgE receptor internalization
- Antibiotic desensitizations can be safely performed in cystic fibrosis patients with very low pulmonary function before or after lung transplant
- A 12-step RDD protocol developed at BWH is the safest and most effective universal protocol that can be used for antibiotics, chemotherapy and biological agent desensitizations based on several hundred cases

Introduction

Adverse reactions to drugs are increasingly recognized as important contributors to disease as well as impediments to the best treatment of various maladies, including dermatological, infectious, autoimmune, and neoplastic disorders. With the development of novel pharmacologic agents and the evolution of personalized treatments based on pharmacogenetic profiling, clinicians must decide which agent is the best for a particular patient with a given disease. Biological agents have greatly improved the treatment of chronic inflammatory diseases and malignancies while limiting some medication-associated toxicities. Because of better outcomes, longer patient survival, and extended treatment courses, patients are exposed to drugs more frequently and for longer time periods, increasing the risk of sensitization to medications. The frequency of adverse drug reactions has increased in the last 10 years. Because of the severity of some reactions and the fear of inducing a potentially lethal reaction in highly sensitized patients, first line treatments are sometimes abandoned, relegating hypersensitive patients to secondary, less effective, therapy. Some of these reactions are mast cell-mediated HSRs, a subset of which occur through an IgE-dependent mechanism, and are thus true allergies. Others involve mast cells, but an IgE mechanism cannot be demonstrated. RDD is a technique that induces temporary tolerance to a drug, allowing a medication-allergic patient to receive the optimal agent for his or her disease. Through RDD, patients with IgE and non-IgE HSRs can safely be administered important medications while minimizing or completely inhibiting adverse reactions.

General Principles and Proposed Mechanisms of Rapid Drug Desensitization

Exposure of IgE-sensitized patients to medication can cause the sudden systemic release of inflammatory mediators from activated mast cells, leading to anaphylaxis.
and medication avoidance, while effective for circumventing an HSR, may lead to significant morbidity and mortality due to suboptimal treatment of disease. RDD is a process by which mast cells are rendered hyporesponsive to an agent that, when administered in typical fashion, induces mast cell activation and degranulation. RDD provides temporary tolerization for drug-hypersensitive patients, protecting them from anaphylaxis. Desensitization protocols have been developed to help deliver full therapeutic doses of drug allergens, in an incremental, stepwise fashion without eliciting life-threatening symptoms [3–5]. Most IgE-sensitized patients present with a positive skin test to the medication, indicating that mast cells (likely through drug-specific IgE) are the main cells responsible for these reactions. After rapid desensitization, specific skin test reactivity is abolished, implying a complete inhibition of the mechanisms that induced mast cell activation [6].

Mast cells activated by antigen crosslinking of IgE-bound FcεRI receptors display aggregation of these receptors, recruitment and activation of target molecules, calcium mobilization, degranulation, arachidonic acid metabolism, and cytokine and chemokine gene transcription [7, 8]. RDD then induces mast cell tolerization to antigen via Internalization of FcεRI. This may occur through progressive crosslinking at low antigen concentration, sub-threshold depletion of mediators, and depletion of activating signal transduction components such as Syk kinase, all of which have been postulated as mechanisms for cellular unresponsiveness to specific activating doses of allergen [9, 10].

To test these hypotheses, we and others developed a reproducible in vitro model of antigen specific, rapid mast cell/IgE desensitization in the presence of physiologic levels of calcium (fig. 1). Increasing doses of antigen delivered at fixed time intervals induced a highly specific and prolonged hyporesponsiveness to triggering doses of the desensitizing antigen. Mast cells desensitized to DNP or OVA antigens demonstrated almost complete inhibition of β-hexosaminidase and preformed TNF-α release, calcium flux, and arachidonic acid metabolism, suggesting a complete abolition of the acute phase of mast cell activation and demonstrating that the subclinical release of mediators was unlikely during human desensitizations. Desensitized mast cells did not release significant amounts of newly generated IL-6 or TNF-α, confirming that during rapid desensitization, patients were not at risk for a delayed reaction due to the lack of late-phase mediator generation.

When mast cells were sensitized to both DNP and OVA antigens, DNP-desensitized cells responded fully to OVA and vice versa, proving antigen specificity and providing evidence that the activating signal transduction pathways are intact for a second allergen. Therefore, the hypothesis that activating signaling molecules are exhausted during rapid desensitization is not supported.

Importantly, antigen-specific IgE bound to the α-chain of FcεRI remained at the membrane level after rapid desensitization, indicating that the lack of reactivity during desensitization was not due to the disappearance of surface IgE and FcεRI when bound to small doses of antigen (fig. 2). Thus, the biochemical mechanism(s) by
which RDD induces mast cell tolerance are still unclear. However, this in vitro model provided an optimal dose-time relationship, leading to almost complete abrogation of early- and late-phase activation events, providing a basis for a modified human rapid desensitization protocol that has been used successfully in hundreds of desensitizations, illustrating the profound inhibition of acute and delayed mast cell responses and the protection against anaphylactic reactions [4, 5].

**Clinical Rapid Desensitization: Protocols and Agents**

The BWH Desensitization Program devised a 12- to 20-step standard protocol based on the above in vitro mouse mast cell model, in which unresponsiveness to a triggering antigen dose was achieved by delivering doubling doses of antigen at fixed time
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intervals starting at 1/1,000 dilution of the final dose [11]. The most commonly used protocol has 12 steps, using three ten-fold diluted solutions at escalating rates (fig. 3). Patients who have had severe anaphylactic reactions to the given agent, or who have reacted early in the standard 12-step desensitization may experience fewer symptoms if desensitized using a 16-step protocol, which adds another bag containing a 1/10,000 dilution of the full dose. The use of a 16-step (4 bags) or 20-step (5 bags) protocol is reserved for high-risk patients (see below). Drug desensitization is more than a protocol; it is an approach to specialized patient care. It thus starts with an allergy evaluation of the patient, including an in-depth historical analysis of the patient’s HSR, skin testing when available, design and testing of an initial desensitization protocol, and adjustment of this protocol in an iterative fashion based on the patient’s response.

Below, we summarize our experience with rapid desensitization to four different classes of drugs: antibiotics, taxane chemotherapy agents, platinum-based chemotherapeutic agents, and monoclonal antibodies and other miscellaneous medications.

Fig. 2. Mast cell antigen/IgE/FceRI complex internalization is inhibited during rapid desensitization but does not impair specific activation. **a** Cells were treated as indicated and the FceRlla and IgE surface expression were analyzed by flow cytometry. The blue line shows the internalization of the antigen/IgE/FceRI during activation as opposed to the red line in which no internalization occurs during desensitizations. **b** Confocal microscopy of cells treated as indicated. Cells activated with OVA (second panel) presented intracellular green fluorescence indicative of antigen internalization while desensitized cells (first panel) presented little internalization. Cells desensitized to OVA responded to DNP (fourth panel), indicating that the desensitization process is highly specific. Adapted from Sancho-Serra et al. [62].
Rapid Drug Desensitization to Antibiotics

Despite a wide selection of antibiotics available for treatment of inpatient and outpatient infections, a single antibiotic often emerges as the preferred choice in a given situation. If the chosen antibiotic is one to which the patient has a history of HSR, but drug resistance, prohibitive intolerances, limited bactericidal or bacteriostatic activity, and poor bioavailability of alternatives pose a risk of uncontrolled infection, desensitization is the best course. Unlike chemotherapy and monoclonal antibodies, antibiotics are usually administered in doses scheduled 6–24 h apart for several days to weeks. This discussion focuses on intravenous rapid desensitization to antibiotics for immediate-type HSRs, and does not include slow oral desensitization regimens that have been described for delayed-type hypersensitivities to multiple antimicrobials, including trimethoprim/sulfamethoxazole, metronidazole, isoniazid, and antiretrovirals.
Experience with antibiotic desensitization, primarily with penicillins and cephalosporins, has accumulated over several decades following a case series describing penicillin desensitization in penicillin-sensitive pregnant women with syphilis [12]. Only immediate-type HSRs consistent with an IgE- and/or mast cell-mediated mechanism are considered amenable to desensitization. Such reactions include dermatologic (flushing, pruritus, urticaria, angioedema), upper and lower respiratory tract (sneezing, sinus and nasal congestion, cough, dyspnea, wheezing), gastrointestinal (abdominal pain, nausea, vomiting, diarrhea), and cardiovascular manifestations (hypotension) during anaphylaxis. Patients with other reactions, including maculopapular rashes, fixed drug eruptions, Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous erythema, drug reaction with eosinophilia and systemic symptoms, transaminitis, acute interstitial nephritis, serum sickness, hemolytic anemia, thrombocytopenia, or neutropenia, are not candidates for rapid intravenous desensitization.

Once an evaluation of the patient determines that the initial reaction is consistent with a mast cell-/IgE-mediated HSR, determining the severity of and the time since the initial reaction makes an assessment of the patient's risk. Penicillin skin testing [reviewed in 13–17] helps in risk-stratifying patients with a history of reaction to penicillin. Such testing has high sensitivity and specificity in estimating the likelihood of reacting to penicillin derivatives and moderate utility in assessing the risk for reacting to cephalosporins, especially first-generation cephalosporins [18, 19]. Following earlier data suggesting high rates of cross-sensitization to carbapenems in penicillin skin test positive patients as measured by imipenem skin testing without challenge [20], systematic imipenem challenge in penicillin skin test positive patients has demonstrated very low true cross-reactivity between these classes [21]. While other studies have described the use of skin testing with non-penicillin antibiotics with increasing data for nonirritating concentrations, none of these testing protocols has been standardized or validated.

The literature on rapid desensitization to antibiotics largely consists of case reports, but several case series in the last decade in cystic fibrosis patients [22–24], a population disproportionately affected by recurrent infections (particularly by Pseudomonas aeruginosa), antibiotic allergies, resistant organisms, and therefore in need of antibiotic desensitization, have established the safety and efficacy of desensitization to various antibiotics. Three studies, including one at our institution, were retrospective chart reviews of patients who underwent desensitization. Success rates ranged from 58 to 100%. Mild to moderate reactions during desensitization did not preclude completion of desensitizations, and could be followed by full scheduled doses. Most patients required multiple desensitizations over time. In our case series, 15 patients completed 100% of 52 desensitizations, 45 without any reaction. Six patients experienced limited symptoms consistent with immediate type HSRs. One patient had acute respiratory failure requiring intubation following ceftazidime desensitization, which was attributed to preexisting infection-related declining respiratory status, and later
had uneventful desensitizations to ceftazidime. In another group of patients, nafcillin, penicillin, cefazolin, and ceftriaxone were among the antibiotics to which patients were successfully desensitized using our protocol [3].

Current recommendations for patients with a history of penicillin reactions who may require penicillin or cephalosporin suggest penicillin skin testing with major and minor determinants when available [25]. Patients with negative skin testing should not require desensitization, and those with positive skin tests are recommended to avoid penicillins and cephalosporins, particularly first-generation agents. If these medications are deemed necessary, desensitization to penicillins and cephalosporins is useful.

Vancomycin is often used in infections with β-lactam resistant Gram-positive organisms or in β-lactam allergic patients. Its use continues to rise with the spread of community and hospital-acquired methicillin-resistant Staphylococcus aureus as well as in persistent and moderate-to-severe cases of Clostridium difficile colitis. Much more common than type I HSRs to vancomycin is red man syndrome (RMS), characterized by flushing, warmth, pruritus, and hypotension. RMS results from direct mast cell and basophil histamine release, can occur without prior exposure, and is not accompanied by an increase in tryptase [26]. While slowing the infusion rate usually ameliorates RMS, true hypersensitivity does not respond to this measure and may require desensitization. Multiple series have been published on successful vancomycin desensitization regimens, both rapid (over hours) and slow (over days) [27–31].

A few reports of ciprofloxacin desensitization exist in the literature [32]. Of the cystic fibrosis patient series described above, our series and that from The Children's Hospital in Boston each include a successful ciprofloxacin desensitization [23, 24]. The Prince Charles Hospital series includes a ciprofloxacin desensitization that was aborted because of an urticarial rash [22].

Hypersensitivity to trimethoprim/sulfamethoxazole most commonly presents as a delayed type cutaneous eruption, and it is a frequent culprit in Stevens-Johnson syndrome. These toxicities are thought to be mediated by reactive metabolites that cannot be fully metabolized by glutathione stores [33]. Slow outpatient oral desensitizations are well-described in patients with HIV/AIDS, who have a disproportionately high prevalence of hypersensitivity to this drug. We have limited experience with patients with the rarer immediate-type HSR, and have successfully performed rapid intravenous desensitizations in such patients [23].

Immediate HSRs to aminoglycosides are also relatively rare. We have described successful intravenous desensitization to tobramycin in a cystic fibrosis patient [23], and the Children's Hospital of Boston series includes a single case of failed gentamicin desensitization [24]. Tobramycin desensitizations via the intravenous and inhaled route have been described previously [34, 35].

Following desensitization, each scheduled full dose of the antibiotic must be administered in a timely fashion in order to prevent loss of the temporary desensitized state.
Rapid Drug Desensitization to Chemotherapeutic Agents: Taxanes

Paclitaxel and docetaxel are widely used in the treatment of ovarian, breast, non-small cell lung, and other solid tumors. HSRs to these taxanes are common: in early trials of paclitaxel, up to 30% of patients developed acute infusion reactions. Premedication with antihistamines and glucocorticoids as well as slower infusion rates have reduced the rate of severe HSRs to less than 10% [36–39]. Similarly, approximately 30% of patients receiving docetaxel without premedication developed acute HSRs, and premedication reduces this rate to less than 10% [40].

Acute HSRs to taxanes are characterized by dyspnea, urticaria, flushing, back or chest severe pain, gastrointestinal symptoms, hypo- or hypertension, and erythematous rashes. Symptoms typically develop within the first few minutes of the infusion, and most often occur on the first or second exposure to the drug [38, 41]. The mechanisms of taxane infusion reactions are not completely understood and may be multifactorial. Proposed mechanisms include complement activation, direct mast cell and/or basophil activation, and IgE-mediated anaphylaxis [42]. Taxane reactions are unlikely to be due solely to an IgE response, because a majority of reactions (56% in one study) occur with the first exposure to paclitaxel, without the prior sensitization necessary for an IgE-mediated reaction [41]. There is evidence that both the taxane moiety itself and the vehicles in which these agents are solubilized can contribute to infusion reactions. Specifically, paclitaxel is stabilized with Cremophor, which is derived from castor oil and is also used as the vehicle for other drugs, such as cyclosporine and vitamin K, which have been associated with similar adverse reactions [41, 43–46]. An albumin-based formulation of paclitaxel, devoid of Cremophor, has also been implicated in HSRs, providing further evidence for taxane moiety-based HSRs.

Desensitization to taxanes is generally well tolerated. In a series of 17 patients who underwent a total of 77 desensitizations to paclitaxel or docetaxel, 72 desensitizations occurred without reactions. Four patients had a total of 5 reactions during desensitization, all of which were much less severe than their original reactions. On the other hand, 5 patients who underwent rechallenge (i.e. readministration of the culprit taxane by regular infusion) prior to desensitization experienced recurrent reactions, despite additional premedication and a reduced infusion rate [47]. In our series of 98 patients undergoing a total of 413 desensitizations to various chemotherapeutic agents, the majority of desensitizations had mild or no reactions, and most reactions occurred during the final, most concentrated solution, and specifically during the last step of the protocol [5].

Rapid Drug Desensitization to Chemotherapeutic Agents: Platinins

The platinum-containing compounds are extensively employed in the treatment of ovarian cancer and other malignancies. Cisplatin was the first to be used, but it was
the relatively low toxicity profile of the second-generation carboplatin that was largely responsible for its increased popularity in the past decade [48]. The third-generation platinum derivative oxaliplatin is widely administered for the treatment of metastatic colorectal cancer. As the use of platinum-containing compounds has increased, so has the incidence of HSRs: cisplatin hypersensitivity varies from 5 to 20%, carboplatin from 9 to 27%, and oxaliplatin from 10 to 19% [49–51]. Unlike the situation with taxanes, repeated exposures are typically required prior to the onset of hypersensitivity to platin. In one study, 50% of the initial HSRs to a platin occurred during the eighth course [52]. Likewise, we found that 40 out of 55 patients with carboplatin HSRs reacted between the 7th and 10th exposure [5]. Cisplatin and oxaliplatin have similar characteristics in that reactions mostly occur between the 4th and 8th course or after the 6th exposure, respectively [51].

The characteristics of HSRs to platinum agents vary widely. In the case of carboplatin, most patients develop cutaneous symptoms, notably palmar or facial flushing. However, half of patients may progress to moderate to severe reactions, and cardiac arrests and deaths have been reported [5]. In our report of 413 desensitizations, of the 60 patients who had carboplatin HSR, 100% had cutaneous symptoms, 57% had cardiovascular symptoms, 40% had respiratory symptoms, and 42% had gastrointestinal manifestations [5].

Oxaliplatin HSRs are often similar to those seen in response to carboplatin and cisplatin, but there have been fewer reports of severe anaphylaxis. However, in contrast to carboplatin, respiratory symptoms are common, and other reactions such as Gell and Coombs type II-mediated thrombocytopenia and Gell and Coombs type III immune-complex-mediated symptoms of chronic urticaria, joint pain, and proteinuria associated, have been reported in response to oxaliplatin. Idiosyncratic reactions to oxaliplatin, including cytokine release syndrome and pulmonary fibrosis, make adverse responses to oxaliplatin heterogeneous and unpredictable [51, 53, 54].

There is a well-recognized association between the interval of carboplatin-free period and the risk of HSR, especially a severe reaction. Schwartz et al. [55] in a study looking at 126 patients with HSR to carboplatin noted that the risk of severe reactions was 47% if the platinum free interval was >24 months, versus only 6.5% if it was <12 months. All 8 patients receiving their third carboplatin regimen had severe reactions.

Skin testing has been used to predict platinum hypersensitivity, but methods vary widely from institution to institution. Our group skin tested 60 patients referred for previous HSRs to carboplatin. Of these, 53 were skin test positive. Of the 7 patients with negative skin tests, 2 converted to positive skin tests after several infusions, one skin test was considered delayed positive, and 4 patients experienced HSRs during infusion [5]. Hesterberg’s group recently published a report of 38 women with carboplatin HSR who were skin tested and desensitized. Thirteen patients were skin test negative to carboplatin, and 7 of those patients had reactions during a rapid desensitization protocol. Interestingly, they found that when dividing the negative skin test group using the time from the HSR to skin testing, those with recent history of HSR
(≤3 months) and negative skin tests did not react, whereas all 7 of the reactors had remote history of HSR (>9 months). Of note, this group uses a maximum carboplatin skin test dose of 3 mg/ml, while our group uses 10 mg/ml.

Patients hypersensitive to a platinum-containing compound or with a positive skin test may be treated by an attempt to readminister the same agent, or the decision may be to change to a different platinum drug, or to be desensitized. The first two choices have produced mixed results, and deaths have been reported. Polyzos et al. [56] reported a series of 32 patients rechallenged with carboplatin after HSRs. Four of the 20 patients with mild reactions again had erythema but were able to finish the medication infusions. However, 12 patients with initial severe reactions including hyper- or hypotension were unable to complete subsequent carboplatin infusions despite prophylaxis. Interestingly in this report, 4 of the 12 were switched to cisplatin and tolerated infusions, but the true incidence of cross-reactivity among platinum-based chemotherapeutic agents is not known. Attempts to circumvent a reaction by switching to another platinum-based chemotherapeutic can be dangerous [56], as exemplified by Dizon et al. [57] who reported the death of one patient due to anaphylaxis in a series of 7 patients switched from carboplatin to cisplatin.

Desensitization has proven to be a safe and effective way to allow a patient to continue carboplatin chemotherapy (see below). Variability in the success rates of desensitization is believed to be due to heterogeneity of methods and protocols.

Rapid Drug Desensitization to Monoclonal Antibodies

Monoclonal antibodies are generally well tolerated treatments for a broad array of diseases, including malignancies and chronic inflammatory conditions. However, a subset of patients experience HSRs following administration of these drugs [58]. Symptoms of such HSRs range from mild (fever, rash, pruritus) to severe, including severe life-threatening anaphylaxis [58].

The rates of HSRs clinically consistent with immediate hypersensitivity to specific monoclonal antibodies have been reported to be 5–10% for rituximab, 2–3% for infliximab, and 0.6–5% for trastuzumab [59]. Immediate HSRs have also been reported for omalizumab, natalizumab, basiliximab, abciximab, and cetuximab. Almost 70% of initial HSRs to monoclonal antibodies include a cutaneous component, the most frequently observed type of reaction overall, followed by cardiovascular, respiratory, and throat tightness [58]. The intensity of reactions to monoclonal antibody infusions is variable. Recent studies have reported that 26% of initial reactions are mild, 48% are moderate, and 26% are severe [59].

Patients with a history suggestive of a mast cell, possibly IgE-mediated HSR should be skin tested with the offending agent as previously described by Lee et al. [6]. HSRs are then classified as mild, moderate, or severe according to the classification system proposed by Brown [60]. Signs and symptoms of HSRs are classified as cutaneous
Protocols for most monoclonal antibodies are generated using the same principles as previously discussed above. Despite its general success, some patients experience HSRs during RDD. In general, these reactions are less intense than the patient’s original reaction. Treatment of such HSRs is aimed at blocking mast cell mediators including histamine, prostaglandins, and leukotrienes [59]. In the event of a reaction during RDD, the infusion is promptly held and the reaction treated. Once the reaction resolves, the protocol can almost always be resumed and completed. The algorithm in figure 4 describes the current approach to monoclonal antibodies hypersensitivity reactions since skin testing positive and negative predictive values are not available for all antibodies. Severe reactions will require desensitization despite negative skin testing.

**Overall Safety and Efficacy**

In 2008, our group reported the largest case series of rapid desensitizations, in which 98 patients with HSRs to chemotherapy underwent 413 desensitizations [5]. In this series, 67% of desensitizations proceeded without HSR, and 27% had only mild reactions (classified as absence of chest pain, changes in blood pressure, dyspnea, oxygen
desaturation or throat tightness), even though 77% of patients had experienced a severe initial HSR. The remaining 6% of desensitizations were characterized by severe HSRs; however, epinephrine was only administered during one desensitization, and there were no transfers to a more acute-care setting, intubations, or deaths. All patients in the case series were able to receive their full target dose.

We subsequently published a case series of 105 desensitizations to monoclonal antibodies in 23 patients [59]. Seventy-four percent of the initial HSRs were moderate to severe. During desensitization, reactions were observed in 29% of desensitizations and 90% of these were mild. Antibiotic desensitization using our protocol is also exceedingly safe [23]: in our case series of 52 antibiotic desensitizations in 15 patients with cystic fibrosis (and a mean FEV1 of 44.1% of predicted), 96.2% of desensitizations were completed without severe adverse events. One patient developed severe acute respiratory failure requiring intubation; however, this was felt to be secondary to worsening pulmonary infection and not a manifestation of a severe HSR during his desensitizations. All desensitizations in this series were completed, suggesting that even markedly impaired baseline lung function is not a contraindication to rapid desensitization.

Treatment of Reactions during Desensitization

In our experience, reactions during desensitization manifest as a wide range of symptoms characteristic of HSRs [59]. Cutaneous reactions may include flushing, pruritus, urticaria and angioedema. More severe reactions may encompass cardiovascular manifestations, such as chest pain, tachycardia, a sense of impending doom, presyncope, syncope and hypotension, as well as respiratory symptoms, including sneezing, nasal congestion, dyspnea, coughing, wheezing, and oxygen desaturation. Severe reactions may also be characterized by throat tightness or gastrointestinal complaints, including nausea, vomiting, diarrhea and abdominal pain. Less common signs and symptoms may include neuromuscular symptoms, such as visual changes, back and neck pain, and numbness/weakness, or, in some cases, fever and chills.

In our 2008 case series of 413 desensitizations in 98 patients, there were a total of 180 reactions, all of which subsided when the infusion was paused and treated appropriately [5]. The majority of reactions (75%) occurred during infusion of solution 3, and 51% of reactions occurred during step 12 of the desensitization protocol. In our monoclonal antibody case series, in which a similar rate of reactions was reported (29%), cutaneous reactions were the most common and, again, the majority of reactions (70%) occurred during step 12. Our approach to treating reactions during desensitization is aimed at blocking local and systemic effects of mast cell mediators, including histamine, prostaglandins, and leukotrienes [59].

At our institution, all reactions during desensitization are treated by pausing the infusion and administering either diphenhydramine or hydroxyzine (25–50 mg administered intravenously) and/or ranitidine (50 mg intravenously). For severe reactions, we
most commonly use methylprednisolone sodium succinate (0.5 mg/kg administered intravenously). We keep epinephrine, 0.3 ml (1 mg/ml) at the bedside. On resolution of the reaction, we restart the protocol from the step at which it had been paused. Patients who experience reactions are then presented and discussed at a weekly meeting of the physicians in our department who perform rapid desensitizations.

We have adopted a two-pronged approach to protocol modification for subsequent desensitizations for patients who react during a prior desensitization [59]. The first component includes administration of additional premedications prior to the start of the protocol or between specific steps during desensitization. Most commonly, these are H1 and sometimes H2 blockers and/or methylprednisolone. These are generally added at least one full step before the point at which the reaction occurred. The second component of our protocol modification involves adding or lengthening steps before the step at which a reaction occurred. This second component is used only when a patient reacts despite additional premedications. By using this approach, we have been able to markedly reduce the rate of reactions over multiple successive desensitizations [5, 59].

Unfortunately, there remains a subset of patients who continue to react during desensitization despite protocol modification and addition of high-dose histamine receptor blockade and corticosteroids. In another case series, we prophylactically treated these patients with oral acetylsalicylic acid (ASA), 325 mg and oral montelukast 10 mg, and were able to successfully treat those patients with refractory mast cell mediator-related symptoms during rapid desensitization [61]. In this study, 78 desensitizations were performed in 14 patients with HSR to platinum chemotherapy that had cutaneous symptoms, many also with associated systemic reactions, during rapid desensitization. Pretreatment with ASA and montelukast 2 days before and on the day of RDD allowed 86% of the patients to tolerate subsequent desensitizations with a less severe or no HSR (fig. 5). Interestingly, only 62% of patients in a control group that received adjunctive methylprednisolone premedication were able to tolerate further desensitizations with a less severe or with no reaction. The greatest benefit of ASA/montelukast pretreatment was seen in patients with skin and respiratory symptoms, suggesting a dominant role for prostaglandins and leukotrienes in these manifestations of HSR to platinum chemotherapies. We have subsequently also treated patients with only one dose of ASA/montelukast 60 min prior to RDD, and have expanded this treatment for use during monoclonal antibody and antibiotic desensitization, and have successfully blocked refractory skin and systemic reactions using this regimen [23, 59].

Conclusions

At our institution, we have had success using an intravenous RDD protocol to treat HSRs to a wide range of medications, including chemotherapeutics, monoclonal antibodies, and antibiotics. Over the past 10 years, more than 99.9% of nearly 800 patients have received the full dose of their first-line medication in thousands of
desensitizations to a wide variety of agents in each of these three classes, and there have been no deaths. Although the molecular basis of RDD remains incompletely understood, an in vitro mast cell model has provided evidence of profound inhibitory mechanisms of mast cell activation during desensitization, which correlates with the remarkable success of the desensitization protocols when used by trained allergists. These safety and efficacy outcomes provide grounds for the continued and expanded use of this RDD approach for all patients for whom a drug hypersensitivity would prevent the administration of first-line pharmacologic therapy.

References


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