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REVIEW

Desensitization regimens for drug allergy: state of the art in the 21st century

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Summary
Adverse reactions to drugs are increasingly being recognized as important contributions to disease in their own right as well as impediments to the best treatment of various conditions, including infectious, autoimmune, and neoplastic maladies. Rapid drug desensitization (RDD) is an effective mechanism for safely administering important medications while minimizing or entirely circumventing such adverse reactions in sensitized patients. We reviewed the literature on RDD in the last 10 years, including our experience from the Brigham and Women's Hospital Desensitization Program with hundreds of patients desensitized to a broad variety of drugs. RDD in our programme has been uniformly successful in patients with hypersensitivity reactions to antibiotics, chemotherapeutics, and monoclonal antibodies. Any reactions that occur during desensitization are generally much less severe than the initial hypersensitivity reaction to the drug, and patients have received the full dose of the desired medication 99.9% of the time out of (796) desensitizations. To date, there have been no fatalities. RDD is a safe and highly effective method for treating sensitized patients with the optimal pharmacologic agents. Its use should be expanded, but because patient safety is paramount, protocols must be created, reviewed, and overseen by allergist–immunologists with special training and experience in modern techniques of desensitization.

Introduction

Innovation to address the need to treat patients with a wide variety of common and important diseases, including infections, malignancies, and arthritides, has brought forth a number of novel pharmacologic agents. With a larger gamut of drugs, clinicians must decide which agent is the best for a particular patient with a given disease, personalizing treatment. Adverse drug reactions, however, are frequently encountered and threaten to relegate the patient to a secondary therapy. Some of these reactions are mast cell-mediated hypersensitivity reactions (HSRs), a subset of which occur through an IgE-dependent mechanism, and are thus true allergies. Rapid drug desensitization (RDD) is a technique that uses protocols that induce temporary tolerance to a drug, allowing a patient with such a drug hypersensitivity to receive the optimal agent for his or her disease.

General principles and proposed mechanisms of rapid drug desensitization

The cell targets for rapid desensitization are thought to be mast cells and possibly basophils. Once mast cells and basophils are sensitized with specific IgE to medications, exposure to the allergen medication can cause the sudden systemic release of inflammatory mediators from activated mast cells, leading to anaphylaxis. RDD is a process by which mast cells are rendered hypo-responsive to a medication allergen by providing temporary tolerization for drug hypersensitive patients, protecting them from anaphylaxis. Desensitization protocols typically include the incremental, stepwise-fashion administration of increasing amounts of the medication allergen without eliciting life-threatening symptoms [1–3].

Research into the mechanisms of RDD has focused largely on patients with a positive skin test to the culprit 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, indicating that the allergen is no longer able to trigger skin mast cell activation and that systemically distributed mast cells have lost the ability to release mediators [4]. Mast cells activated by antigen cross-linking 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 [5, 6]. Three non-mutually

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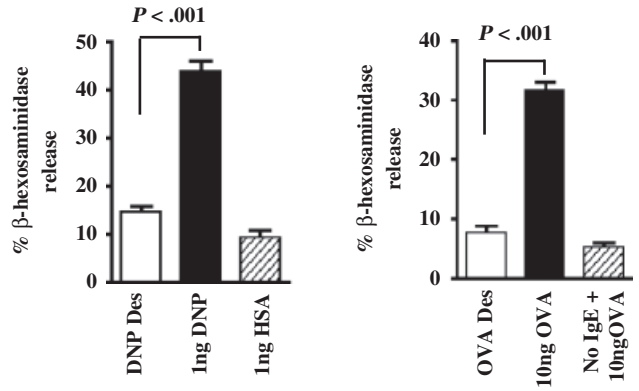

Fig. 1. Desensitization inhibits the release of mast cell granule mediators. Release of granule mediators (β-hexosaminidase) after DNP and ovalbumin (OVA) antigens activations in bone marrow mouse mast cells and after desensitization (DNP desensitization and OVA desensitization). Adapted from Sancho-Serra et al. [67].

exclusive hypotheses explaining how RDD could impair mast cell activation have been articulated: (1) depletion of activating signal transduction components such as syk kinase, (2) sub-threshold depletion of mediators, and (3) internalization of FcεRI through progressive cross-linking at a low antigen concentration [7, 8].

Ubiquitination of syk after prolonged exposure to sub-threshold doses of antigen is one mechanism for inducing unresponsiveness of basophils and mast cells, but this process is unlikely to explain the efficacy of rapid desensitizations because the antigen exposure during desensitization does not allow sufficient time for this to occur.

An *in vitro* model of antigen-specific, rapid mast cell/IgE desensitization in the presence of physiologic levels of calcium was developed (Fig. 1). Increasing doses of antigen delivered at fixed time intervals induced a highly specific and prolonged hypo-responsiveness to triggering doses of the desensitizing antigen. The release of granules mediators such as β-hexosaminidase and the metabolism of arachidonic acid products such as prostaglandins and leukotrienes were inhibited by desensitization (Figs 1 and 2). The desensitization process was achieved by incremental doses administered at fixed time intervals and did not produce a slow release of mediators as mast cells responded well to further allergen stimulation after each of the desensitizing doses (Fig. 3). As long as the antigen was maintained, the desensitization was maintained, indicating that the presence of allergen was necessary (Fig. 4). Mast cells desensitized to DNP antigen demonstrated almost complete inhibition of release of pre-formed and newly generated TNF and IL-6, explaining why patients are not at a risk for a delayed reaction after rapid desensitization, as late-phase mediator generation does not occur (Fig. 5). When mast cells were sensitized to both DNP and OVA antigens, OVA-desensitized cells responded fully to ONP, proving antigen specificity and providing evidence that the activating signal transduction pathways

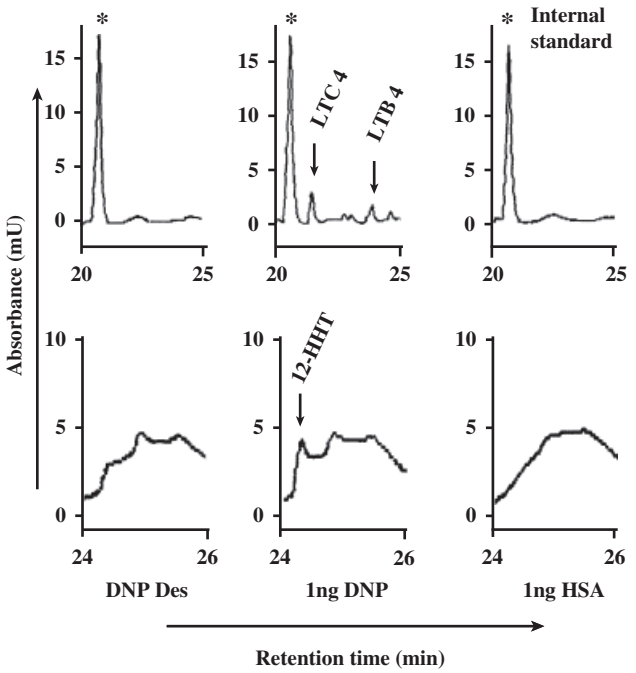

Fig. 2. Desensitization inhibits the metabolism of arachidonic acid and the generation of prostaglandins and leukotrienes. Upper panel: LTC4 and LTB4 peaks during activation and desensitization. Lower panel: 12 HHT (prostaglandin pre-cursor) during activation and desensitization. Adapted from Sancho-Serra et al. [67].

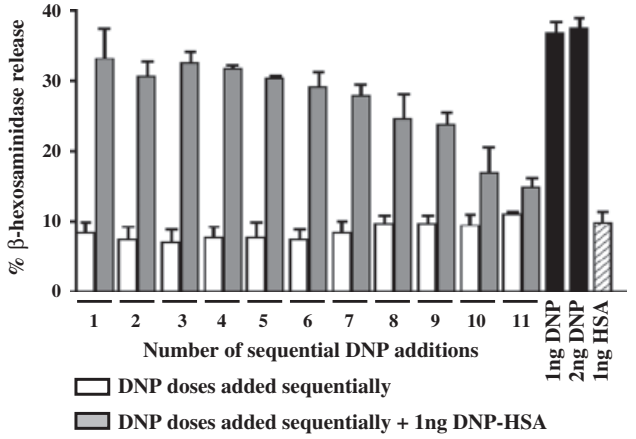

Fig. 3. Desensitization of BMMC required multiple sequential doses and does not induce mediator depletion. Release of granule mediators (β-hexosaminidase) after sequential doses of DNP antigen (1 through 11) ± 1 activating dose of DNP. Adapted from Sancho-Serra et al. [67].

are intact for a second allergen (Fig. 6). Therefore, the hypothesis that activating signalling molecules are exhausted during rapid desensitization is not supported. Importantly, antigen-specific IgE bound to the α-chain of FcεRI remained at the cell surface after rapid desensitization, indicating that the lack of reactivity during desensitization was not due to the disappearance of surface IgE and FceRI when bound to small doses of antigen (Fig. 6). Thus, although these models recapitulated the profound

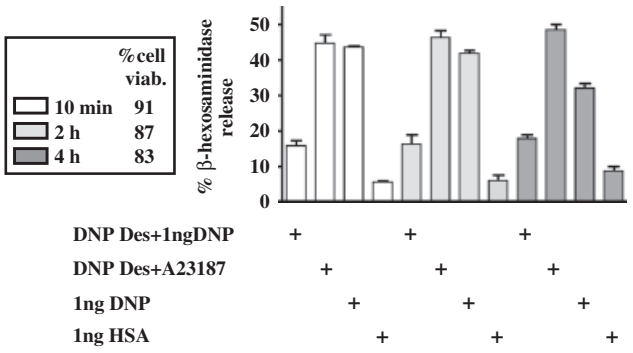

Fig. 4. Desensitization is maintained as long as antigen is present. Release of granule mediators (β-hexosaminidase) after desensitization, 2 and 4 h later. Adapted from Sancho-Serra et al. [67].

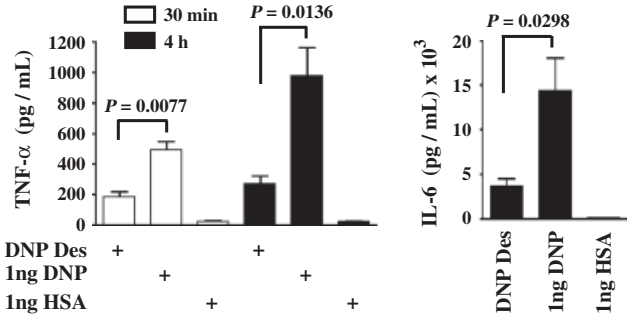

Fig. 5. Desensitization inhibits acute- and late-phase cytokines TNF- and IL-6. TNF-α and IL-6 were measured in the supernatants after the activation and desensitization of BMMC. Adapted from Sancho-Serra et al. [67].

inhibition of acute and delayed mast cell responses that provide protection against anaphylactic reactions, and provided the basis for an adapted protocol that has been applied to hundreds of successful desensitizations, they have not shed light on the mechanisms actually responsible for mast cell hypo-responsiveness [2, 3].

General principles of rapid drug desensitization

The BWH Desensitization Program devised a 12- to 20-step standard protocol based on an *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 intervals starting at 1/1000 the final dose [9]. The most commonly used protocol has 12 steps, using three solutions at escalating rates (Fig. 7). Patients who have had severe anaphylactic reactions to the agent of choice 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 1/1000th of the full dose. The use of a 16-step (four bags) or a 20-step (five bags) protocol is reserved for high-risk patients. Common side-effects include flushing, warmth, pruritus, erythema, and urticaria, and patients are cautioned about the low but real risk of anaphylaxis.

Our standardized desensitization protocol has been described previously [1]. Routine premedication consists of a single dose each of diphenhydramine and famotidine. Specific tailoring of a protocol may include the addition of aspirin, montelukast, or glucocorticoids to the pretreatment regimen based on previous symptoms of flushing or throat itching. β-adrenergic blocking medications are held for 24 h before desensitization. An essential point is that a thoughtful approach to drug hypersensitivity and RDD requires more than the standard desensitization protocol. No rigid algorithm, no matter how widely applicable, will suffice. Instead, our dynamic and flexible practice is to follow these steps:

1. evaluate the patient, attempting to characterize the nature of a patient's adverse reaction,
2. determine the likelihood that RDD will be effective and safe,
3. apply or design a reasonable RDD protocol (often using our standard 12-step protocol as a starting place),
4. collect information about how the patient responds to each desensitization and modify the protocol as needed:

(a) adding, subtracting, or changing premedications,
(b) changing the number of steps in the protocol,
(c) altering the rate or time of one or more steps, and
(d) some combination of these.

Thus, drug desensitization truly begins with an analysis of the patient's HSR, design and testing of an initial desensitization protocol, and adjustment of this protocol in an iterative fashion based on the patient's response. Adverse drug reactions inducing a type I hypersensitivity reaction, whether IgE or non-IgE mediated, are eligible for rapid desensitizations. The symptoms of these reactions include cutaneous (flushing, pruritus, urticaria or angioedema, maculopapular rash), respiratory (nasal congestion, sneezing, wheezing, shortness of breath, cough, O_2 desaturation), gastrointestinal (nausea, vomiting, diarrhoea, abdominal pain, bloating), cardiovascular (chest pain, tachycardia, presyncope syncope, hypertension, hypotension, EKG changes), neuromuscular (sense of impending doom, disorientation/hallucination, visual disturbances, unusual taste, back pain, numbness/weakness), and/or throat tightness during the infusion or shortly after the administration of these medications. Because rapid desensitization does not result in long-term tolerance, patients need to be re-desensitized each time they are exposed to the allergenic medication. If the medication is maintained at pharmacological levels by daily

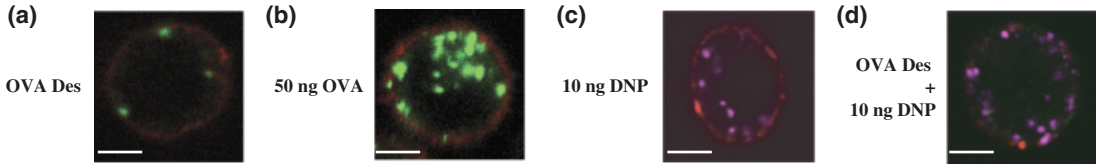

Fig. 6. Desensitization is antigen specific and prevents the internalization of the antigen/IgE/FceRI complex. Internalization is seen after ovalbumin (OVA) activation (b), but not with desensitization (a), and DNP is internalized after activation in OVA-desensitized cells, which is comparable to that of DNP-HSA active cells (d). Adapted from Sancho-Serra et al. [67].

Name of medication:		***Remicade***					
Target dose (mg)				800			
Standard volume per bag (mL)				250			
Final rate of infusion (mL/hr)				80			
Calculated target concentration (mg/mL)				3.2			
Standard time of infusion (min)				187.5			
					Total mg per bag	Amount of bag infused (mL)	
Solution 1	250	mL of	0.032	mg/mL	8.000	9.25	
Solution 2	250	mL of	0.320	mg/mL	80.000	18.75	
Solution 3	250	mL of	3.175	mg/mL	793.704	250.00	
*** PLEASE NOTE ***		The total volume and dose dispensed are more than the final dose given to patient					
			because the initial solutions are *not completely infused*				
Step	**Solution**	**Rate (mL/h)**	**Time (min)**	**Volume infused per step (mL)**	**Dose administered with this step (mg)**	**Cumulative dose (mg)**	Fold increase per step
1	1	2.0	15	0.50	0.0160	0.0160	–
2	1	5.0	15	1.25	0.0400	0.0560	2.5
3	1	10.0	15	2.50	0.0800	0.1360	2
4	1	20.0	15	5.00	0.1600	0.2960	2
5	2	5.0	15	1.25	0.4000	0.6960	2.5
6	2	10.0	15	2.50	0.8000	1.4960	**2**
7	2	20.0	15	5.00	1.6000	3.0960	2
8	2	40.0	15	10.00	3.2000	6.2960	**2**
9	3	10.0	15	2.50	7.9370	14.2330	2.480325
10	3	20.0	15	5.00	15.8741	30.1071	**2**
11	3	40.0	15	10.00	31.7482	61.8553	2
12	3	80.0	174.375	232.50	738.1447	800.0000	2
	Total time (min) =		339.375	= 5.66 h			

Fig. 7. A standard 12-step, three-bag desensitization protocol from the Brigham and Women's Hospital Rapid Drug Desensitization Program.

administration, such as with aspirin desensitization intended for daily use for cardio-protection or during an antibiotic course in which the antibiotic is given at regular intervals, the desensitized state is maintained. *In vitro* experiments confirm that maintaining the presence of the allergen preserves mast cell unresponsiveness. For medications given at intervals significantly greater than their half-lives, such as monoclonal antibodies and chemotherapeutic agents, desensitization needs to be repeated for each administration.

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

Rapid drug desensitization to antibiotics

Despite a wide selection of antibiotics available for the treatment of inpatient and outpatient infections, a single

antibiotic often emerges as the preferred choice in a given situation. Not infrequently, the antibiotic chosen is one to which the patient has a history of HSR. Drug resistance, prohibitive intolerances, limited bactericidal or bacteriostatic activity, and poor bioavailability of alternatives pose a risk of uncontrolled infection that outweighs those of desensitization. Unlike chemotherapy and monoclonal antibodies, antibiotics are usually administered over a course of several days to weeks in doses scheduled 6–24 h apart. When considering antibiotic desensitization, one must verify that regular dosing of the antibiotic for the intended duration of therapy following desensitization can be maintained, as RDD effects a temporary state of tolerance, and premature cessation of the antibiotic may require re-desensitization before the completion of a course. 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/sulphamethoxazole, 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 [10]. Only immediate-type hypersensitivity reactions consistent with an IgE- and/or mast cell-mediated mechanism are considered amenable to desensitization. Such reactions include dermatologic (flushing, pruritus, urticaria, angiooedema), upper and lower respiratory tract (sneezing, sinus and nasal congestion, cough, dyspnoea, wheezing), gastrointestinal (abdominal pain, nausea, vomiting, diarrhoea), 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 (DRESS), transaminitis, acute interstitial nephritis, serum sickness, haemolytic anaemia, thrombocytopenia, or neutropenia, are not candidates for rapid intravenous desensitization.

The decision to embark upon antibiotic desensitization should be made in conjunction with an Infectious Diseases specialist to determine the relative advantages of first-line therapy over alternatives, the duration of treatment, and the goals of therapy. Evaluating the patient for desensitization requires taking a careful history to determine whether the initial reaction is consistent with a mast cell-/IgE-mediated hypersensitivity reaction, and assessing the patient's risk by determining the severity of and the time since the initial reaction. With the renewed availability of the major determinant penicilloyl polylysine, skin testing has once again become a validated component of the assessment of β-lactam allergies and can be particularly useful in patients with vague histories. Penicillin skin testing (extensively reviewed elsewhere [11–15]) provides a method of risk-stratifying patients with a history of reaction to penicillin. The penicillin skin test with the major and minor determinants of penicillin has a high negative predictive value [16, 17]. 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 [18], a systematic imipenem challenge in penicillin skin test-positive patients has demonstrated very low true cross-reactivity between these classes [19]. While other studies have described the use of skin testing with non-penicillin antibiotics with increasing data for non-irritating concentrations, none of these testing protocols has been standardized and validated.

The literature on rapid desensitization to antibiotics largely consists of case reports, but there have been several case series in the last decade in cystic fibrosis patients [20–22], a population disproportionately affected by recurrent infections (particularly by *Pseudomonas aeruginosa*), antibiotic allergies, resistant organisms, and therefore in need of antibiotic desensitization. These studies provide data on the safety and feasibility of desensitization to various antibiotics, primarily β-lactams, in a high-risk population with poor lung function. All three studies, including one at our institution, were retrospective chart reviews of patients who underwent desensitization. Success rates ranged from 58% to 100%. Differences among the studies include patient age, nature of prior reactions, premedications, protocol including the starting dose and the rate of increase, definition of desensitization success, and threshold to stop desensitization. Mild to moderate reactions during desensitization did not preclude the 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 hypersensitivity reactions. 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 [1].

Current recommendations for patients with a history of penicillin reactions who may require a penicillin or cephalosporin suggest penicillin skin testing with major and minor determinants when available [23]. 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 may be quite useful in skin test-positive patients.

Although vancomycin is not the preferred agent for the treatment of β-lactam-susceptible infections, it is used in gram-positive infections with β-lactam resistance or in β-lactam-allergic patients. Its use continues to rise with the spread of community and hospital-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) as well as in persistent and moderate-to-severe cases of *Clostridium difficile* colitis. Much more common than type I hypersensitivity reactions to vancomycin is the '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 [24]. While slowing the infusion rate usually ameliorates RMS, true hypersensitivity does not respond to this measure and may require desensitization. In addition to the several patients described in the three cystic fibrosis series, multiple series have been published on vancomycin desensitization regimens, both rapid (over hours) and slow (over days), and have been used successfully [25–29].

Fluoroquinolone hypersensitivity is less well understood, and there are few reports of ciprofloxacin desensitization in the literature [30]. Of the cystic fibrosis patient series described above, our series and the Boston Children's Hospital series each include a successful ciprofloxacin desensitization [21, 22], and the Prince Charles Hospital series includes a ciprofloxacin desensitization that was aborted because of a urticarial rash [20].

Hypersensitivity to trimethoprim/sulphamethoxazole 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 [31]. 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 [21].

Immediate HSRs to aminoglycosides are also quite rare, and aminoglycoside use is generally limited by vestibulo/ototoxicity and nephrotoxicity. We have described successful intravenous desensitization to tobramycin in a cystic fibrosis patient [21], and the Children's Hospital series includes a single failed gentamicin desensitization [22]. Tobramycin desensitizations via the intravenous and inhaled route have been described previously [32, 33].

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. As many penicillins have relatively short half-lives, careful consideration should be exercised when contemplating desensitization.

Rapid drug desensitization to chemotherapeutic agents: taxanes

Paclitaxel and docetaxel are cytotoxic drugs widely used in the treatment of ovarian, breast, non-small-cell lung, and other solid tumours. Hypersensitivity reactions to 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 hypersensitivity reactions to $< 10\%$ [34–37]. Similarly, approximately 30% of patients receiving docetaxel without premedication developed acute hypersensitivity reactions, and premedication reduces this rate to $< 10\%$ [38].

Acute hypersensitivity reactions to taxanes are characterized by dyspnoea, urticaria, flushing, back 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 the second exposure to the drug [36, 39].

The characteristics of hypersensitivity reactions to paclitaxel and carboplatin are compared and contrasted in Fig. 8 [3, 40]. Both of these agents frequently cause cutaneous, cardiovascular, and gastrointestinal symptoms. However, while back pain is a frequent symptom in paclitaxel hypersensitivity reactions (36% of patients in this series), it is seldom seen in carboplatin reactions [3]. The mechanisms underlying these differences in presentation are not well understood.

Data on cross-reactivity of paclitaxel and docetaxel have been inconsistent. Previous small clinical trials (3–4 patients each) have described successful treatment with docetaxel following hypersensitivity reactions to paclitaxel [41, 42]. However, a more recent retrospective review found that nine out of 10 patients treated with docetaxel following a hypersensitivity reaction to paclitaxel also reacted to docetaxel, suggesting a higher rate of cross-reactivity [43].

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 [44]. 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 [39]. 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,

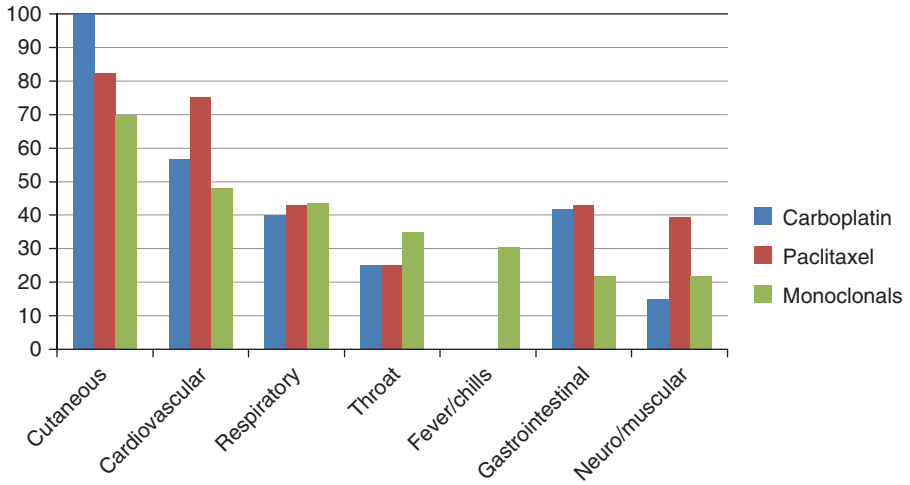

Fig. 8. Symptoms and signs of hypersensitivity reactions in 111 patients. (Adapted from Castells et al. [3] and Brennan et al. [40].)

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 [39, 45–48]. An albumin-based formulation of Paclitaxel, devoid of cremophor, has also been implicated in hypersensitivity reactions, providing further evidence for taxane moiety-based hypersensitivity reactions.

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 five reactions during desensitization, all of which were much less severe than their original reactions. On the other hand, five patients who underwent re-challenge before desensitization experienced recurrent reactions, despite additional premedication and a reduced infusion rate [49]. 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 [3].

Rapid drug desensitization to chemotherapeutic agents: platins

Platinum-containing compounds are some of the most biologically active cytotoxic drugs in the treatment of ovarian cancer, and have been used in the treatment of numerous malignancies since the 1970s. Cisplatin was the first to be used, but it was the relatively low toxicity profile of the second-generation carboplatin that is largely responsible for its increased popularity in the past decade [50]. The third-generation platinum derivative oxaliplatin is widely used for the treatment of metastatic colorectal cancer as well as other malignancies.

As the use of platinum-containing compounds has increased, so has the incidence of HSRs. The reported incidence of cisplatin hypersensitivity varies from 5 to 20%, carboplatin from 9% to 27%, oxaliplatin from 10% to 19% [51–53]. One salient feature of the platinum drugs is the requirement of repeated exposures before the onset of the hypersensitivity. Markman et al.[54] reported that of the 12% of patients receiving carboplatin who had an HSR, 50% of the initial episodes occurred during the eighth course. Other studies have corroborated these data as well. In one retrospective chart review at The University of Texas M.D. Anderson Center, the incidence of carboplatin HSR was 7.9% for ovarian cancer patients. In concordance with previously published data, those patients with carboplatin HSR on average received eight prior doses of carboplatin. Dividing the patients into those who had received $\geqslant 8$ cycles vs. those with <8, the incidence of HSR to carboplatin was 10.7% vs. 1.3%, respectively. Similarly, in ovarian cancer, the incidence of HSR in newly diagnosed patients was 2.1% vs. 17% among those with persistent/progressive disease and 12.6% in patients with recurrent disease [55]. Our group found that 40 out of 55 patients with carboplatin HSRs reacted between the 7th and the 10th exposure [3]. Cisplatin and oxaliplatin have similar characteristics in that reactions mostly occur between the 4th and the 8th course or after the 6th exposure, respectively [53].

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 the patients may progress to moderate to severe reactions, and cardiac arrest and deaths have been reported [3]. 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 (see Fig. 8) [3].

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 often the most common. Maindrault-Goebel and colleagues reported that of 42 patients with oxaliplatin HSR, 50% had respiratory symptoms including laryngeal spasms and hypoxaemia, whereas 40% of patients had cutaneous manifestations. Interestingly, they also reported three cases of a Gell and Coombs type II-mediated thrombocytopenia, and other authors have reported Gell and Coombs type III immune-complex-mediated symptoms of chronic urticaria, joint pain, and proteinuria associated with oxaliplatin. Idiosyncratic reactions to oxaliplatin, including cytokine release syndrome and pulmonary fibrosis, make adverse responses to oxaliplatin heterogeneous and unpredictable [53, 56, 57].

Being able to predict who is at a significant risk of a hypersensitivity reaction would allow for interventions before any adverse outcomes from platinum-containing compounds, without needlessly stopping or withholding medication from those at a low risk. It is clear that in the case of carboplatin, the risk of reaction increases sharply with the 8th exposure, which, in standard protocols, is generally the second cycle of the second treatment regimen. One group also noticed an association between the interval of a carboplatin-free period and the risk of HSR, especially a severe reaction. Schwartz and colleagues, 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, vs. only 6.5% if it was <12 months. All eight patients receiving their third carboplatin regimen showed severe reactions [58].

Using clinical characteristics to stratify risk has been attempted, generally with modest results. One group noted a statistically significant increase in the risk of reaction in patients with a past history of other allergic reactions to either medications or environmental allergens [59]. For oxaliplatin, Kim et al. [60] found that younger age, female sex, and the use of oxaliplatin as salvage therapy were all statistically significant risk factors for an HSR.

Skin testing has been used to predict platinum hypersensitivity, but methods vary widely from institution to institution. Markman and colleagues attempted to identify patients at risk of an HSR before a clinical reaction by performing prospective skin testing 1 h before the 7th cycle of carboplatin. They reported a negative predictive value of 98.5% (658/668). Of the 10 patients who reacted despite having negative skin testing, all of them had only mild cutaneous symptoms. There were 41 patients with positive skin tests, of whom seven were rechallenged, with six of the seven experiencing mild to moderate symptoms.

Our group skin tested 60 patients referred for previous HSRs to carboplatin. Of these, 53 were skin test positive. Of the seven with negative skin tests, two patients converted to positive skin tests after several infusions, one skin test was considered delayed positive, and four patients experienced hypersensitivity reactions during infusion [3].

Hesterberg and colleagues 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 seven 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 a recent history of HSR (<3 months) and negative skin tests did not react, whereas all seven of the reactors had a 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.

Once a patient has an allergic reaction to a platinum-containing compound or a positive skin test, the physician must then decide whether to attempt re-administration of the same agent, to change to a different platinum drug, or to desensitize the patient. The first two choices have produced mixed results, and deaths have been reported. Polyzos and colleagues 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, four 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 [61], as exemplified by Dizon et al. [62], who reported the death of one patient due to anaphylaxis in a series of seven patients switched from carboplatin to cisplatin.

A plethora of literature attests to the safety of desensitization as a way to allow a patient to continue carboplatin chemotherapy. However, there is variability in the success rates due to the fact that platinum desensitization is not standardized, and different institutions follow various methods and protocols. O'Cearbhaill and colleagues prophylactically converted 174 patients to an extended infusion schedule after the 8th cycle, with 1% of the dose administered in the first hour, 9% during the second hour, and 90% during the third hour. Of the 174 patients converted to this schedule, only six (3.4%) developed HSR vs. 111/533 (21%) of those remaining on a standard infusion protocol. An important caveat to these results is that this was a retrospective study, and so potential confounding factors such as premedications administered, prior drug allergy history, or number of infusions may not have been controlled for between the two groups [63].

Rapid drug desensitization to monoclonal antibodies

Monoclonal antibodies are rapidly becoming standard therapy in the treatment of a multitude of diseases. For the most part, they are well tolerated. However, a subset of patients experience HSRs following the administration of these drugs [64]. The symptoms of HSRs range from mild (fever, rash, pruritus) to severe, including severe life-threatening anaphylaxis [64].

The rates of HSRs that are clinically consistent with immediate hypersensitivity to monoclonal antibodies and other drugs considered in this section have been reported to be 5–10% for rituximab, 2–3% for infliximab, and 0.6–5% for trastuzumab [40]. Immediate HSRs have also been reported for omalizumab, natalizumab, basiliximab, abciximab, and cetuximab.

Cutaneous reactions were observed as a component of almost 70% of the initial reactions and were the most frequently observed type of reaction overall, followed by cardiovascular, respiratory, and throat tightness [64]. The intensity of reactions to monoclonal antibodies infusions is variable. Recent studies have reported that 26% of the initial reactions are mild, 48% are moderate, and 26% are severe [40]. Demographic studies have reported a markedly increased incidence of severe HSRs among patients living in the middle portion of the southeastern United States. One study recorded a rate of severe HSRs as high as 3% [65]. Follow-up studies of patients treated with cetuximab in clinical trials in Tennessee and North Carolina showed a rate of severe HSRs of 22% [66]. When the authors tried to identify associations between HSRs and risk factors including demographics, primary sites of cancer, and atopic history, only atopic history was significantly associated with the severe HSRs [66].

Patients with a history suggestive of a mast cell, possibly IgE-mediated HSR, should be skin tested with the offending agent as described previously [40]. HSRs are then classified as mild, moderate, or severe according to the classification system proposed by Brown [40]. Fever and/or chills, which are not included in the Brown classification, are classified as mild for subjective fever, or a measured $T < 38.0\,^{\circ}\mathrm{C}$. $T > 38.0\,^{\circ}\mathrm{C}$ was classified as a moderate reaction. The signs and symptoms of HSRs are classified as cutaneous (flushing, pruritus, urticaria, angiooedema), cardiovascular (chest pain, tachycardia, sense of impending doom, presyncope, syncope, and hypotension), respiratory (dyspnoea, wheezing, and oxygen desaturation), throat tightness, gastrointestinal (nausea, vomiting, diarrhoea, and abdominal pain), neurological/muscular (vision disturbances, back and neck pain, and numbness/weakness), and fever/chills [40].

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 [40]. In the event of a reaction during RDD, the infusion is promptly held. Further reactions are managed clinically based on the algorithm in Fig. 9.

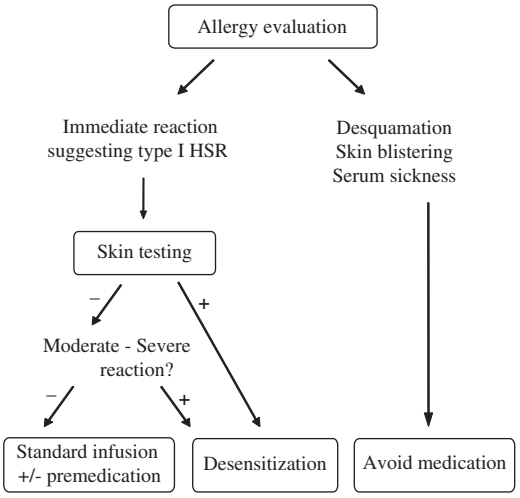

Fig. 9. Algorithm for the assessment and treatment of patients with HRS (from Brennan et al. [40]).

Recent data show reactions rates of 29% during monoclonal antibody desensitization, with 90% of these reactions being mild [40]. In the small percent of cases that had a severe reaction, all patients retrospectively had positive skin testing to the agent administered [40] As expected, cutaneous reactions were the most frequent type of reaction observed during desensitization. It was also observed that 70% of reactions during desensitization occurred during the 12th and the final step using our standard 12-step protocol [40]. Delayed reactions have been reported but to date these reactions have all been mild [40].

Conclusions

Although the molecular basis of RDD is not completely understood, the protocols have been remarkably successful. 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, and there have been no deaths from HSRs [3]. These safety and efficacy outcomes provide grounds for the continued and expanded use of this approach to RDD for all patients for whom a drug hypersensitivity would prevent the administration of first-line pharmacologic therapy. Using a standardized BWH 12-step protocol, we have been able to treat hundreds of patients with infections, cancer, and inflammatory conditions, providing improved quality of life and increased survival rates. This desensitization protocol is an innovative and useful tool for all medical specialties when applied under the supervision of trained allergists.

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