

A New Era for Drug Desensitizations

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Drug desensitizations have become a cornerstone of the treatment of patients with drug-induced hypersensitivity reactions in the 21st century, emphasizing the critical need for allergists to assist all medical specialties in evaluating patients allergic to their best medications.¹ Drug desensitizations are aimed at reintroducing a potentially dangerous medication in a controlled fashion in highly sensitized patients to increase their life expectancy or the quality of their life.² Rapid drug desensitization (RDD) protocols address type I reactions with mast cell/basophils/IgE involvement, and slow drug desensitization protocols address delayed type IV reactions with T-cell involvement. Mixed reactions are seen with increasing frequency with patients presenting urticarial rashes in a delayed fashion, and RDD protocols have been used for delayed reactions with great success, changing the paradigm of the segregation and use of RDD versus slow drug desensitization.³ Some of the mechanisms and kinetics of IgE rapid desensitization have been established experimentally *in vitro* and *in vivo* and have been used to generate protocols for human use. Mouse and humanized mast cells have been desensitized through IgE/FcεRI receptors by doubling doses of antigen delivered every 10 minutes or more until reaching the target dose, without release of mediators, prostaglandins, leukotrienes, or cytokines.⁴ Mice have been specifically desensitized to ovalbumin and dinitrophenyl phosphate antigens through similar protocols, protecting them from anaphylaxis and death.⁵ The initial success applying these protocols to human desensitizations² opened the field to the wide use of drug desensitizations for each patient in need and for each drug that induced a hypersensitivity reaction.⁶ Part of the success is due to the careful evaluation of candidate patients, divided into 2 broad categories: (1) patients presenting with acute symptoms during or shortly after the infusion, injection, or ingestion of the medication and presenting with type I symptoms compatible with mast cell/basophil/IgE mechanisms with release of mediators such as tryptase, and (2) patients presenting with delayed symptoms attributed to T cells with maculopapular rashes. Type I and type IV reactions are amenable to desensitizations because modulation of mast cell/basophil and T-cell responses take

advantage of already existing interactions between activatory and inhibitory pathways. In contrast, patients with Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, and acute generalized exanthematous pustulosis are not considered candidates for drug desensitization because specific HLA haplotypes segregate the reactive patient population such as in the case of abacavir for HLAB5701.⁷ Although not proven, minuscule amounts of medication, such as provided during desensitization, could bind HLA molecules and trigger a reaction for which no inhibitory pathways are known.

This issue of *The Journal of Allergy and Clinical Immunology: In Practice* provides evidence of the extended reach and impact of new desensitization protocols applied to a wide range of severe disease, underscoring the wide potential for their applications to new drugs as more safety data become available. Two categories are presented: the first 3 articles describe new desensitizations for type I reactions, and the last 2 articles describe desensitizations for type IV local and systemic reactions.

Tsilochristou et al⁸ report the success of rapid desensitization in a 22-year-old woman with Gaucher disease type I, the most common form of the disease affecting 90% of the patients, where a defect in the production of lysosomal glucocerebrosidase leads to the accumulation of glucosylceramide-laden macrophages in tissues and organs including bone, hematological abnormalities, and shortened life span. Intravenous imiglucerase replacement for 2.5 years at 30 U/kg every 2 weeks halted the progression of disease until severe flushing, headache, and tachycardia, unresponsive to antihistamines and slow infusion rates, occurred. A change to miglustat for several months was complicated by disease progression, and the reintroduction of imiglucerase produced an anaphylactic episode. Skin test result was positive, and a 3-bag 12-step desensitization protocol was generated by targeting the optimal dose and was implemented in less than 6 hours. The patient tolerated the protocol with minimal symptoms and continued to receive the medication through the protocol every 2 weeks.

Garcia Escallon et al⁹ describe a 79-year-old woman with small cell lung carcinoma who presented during her second chemotherapy cycle 5 minutes into the etoposide infusion with an anaphylactic reaction characterized by dyspnea, tachycardia, hypotension, generalized pruritus, and oxygen desaturation with feeling of impending doom. No tryptase levels or skin tests were obtained, and the patient was desensitized using a novel 3-bag 12-step protocol with 2 additional steps (14 steps) to provide slower incremental infusion rates due to the severe initial reaction. Premedications included dexamethasone and epinephrine, and the total infusion time was more than 15 hours. The patient had no reaction during the protocol and was desensitized 3 times successfully until the disease progressed and the treatment changed.

Jean and Kwong¹⁰ describe a 13-year-old boy with acute lymphoblastic leukemia desensitized to voriconazole who

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presented an anaphylactic reaction following the first exposure. The patient had consolidation chemotherapy and developed a febrile disease treated with micafungin and developed within minutes of the first dose wheezing, face angioedema, and full body pruritic rash, which required epinephrine and steroids. Within 28 hours he was treated with voriconazole and developed similar symptoms. Skin test demonstrated an IgE-mediated reaction, and the patient was treated with a 14-step desensitization protocol with doubling doses, reaching the target dose in 3 hours, and was successfully maintained for 10 days without further symptoms.

Di Paolo et al¹¹ presented 2 cases of febuxostat desensitization for type IV delayed reactions. Febuxostat is a new nonselective xanthine oxidase inhibitor for patients with severe reactions to allopurinol and/or presenting the susceptibility haplotype HLAB5801. A 79-year-old man with renal cell carcinoma, hyperuricemia, and gout presented a severe maculopapular rash 3 days after starting febuxostat at 80 mg and was desensitized in 5 days with 1.5 times to doubling doses for 12 total doses and was able to be maintained for the length of follow-up. Interestingly, during the dose escalation he manifested urticaria, which resolved with continued dosage. A 65-year-old man with chronic gout and Lyell syndrome induced by allopurinol was treated with febuxostat for 4 days and developed a maculopapular rash. He was desensitized with a similar protocol but required 27 days to reach the target dose of 80 mg and was able to be maintained without further rashes.

Bavbek et al¹² provide the largest series of patients successfully desensitized to subcutaneous etanercept and adalimumab for type I and type IV reactions. The patients were sensitized through subcutaneous injections, 6 to etanercept presenting with systemic reactions including anaphylaxis and negative skin test results and 6 to adalimumab presenting with large local reactions and positive skin test results. Patients desensitized to adalimumab achieved their target dose with 12 steps and were able to be maintained on every 2-week doses with minimal local erythema at the site of injections. Etanercept patients were able to receive their target dose using a 7-step doubling protocol and were treated weekly without systemic adverse effects.

Some of the initial reactions to medications described above are systemic, including anaphylactic manifestations, and yet the new desensitization protocols are able to provide unprecedented protection through the critical principle of all desensitizations, which is that doubling doses of medication trigger inhibitory mechanisms that protect patients against anaphylaxis. Younger patients are being desensitized successfully, as shown by Tsilochristou et al,⁸ providing evidence that there is no age limitation for desensitizations. Improving the quality of life is one of the

goals of drug desensitizations, and the cases described in this issue reflect a need for evaluation of sustained desensitizations for imiglucerase, etanercept, adalimumab, febuxostat, and etoposide, which should be addressed in future studies. Can desensitization protocols be modified to safely provide the needed medication in shorter times? Are patients receiving multiple desensitizations generating tolerance mechanisms to their desensitizing medications? Research and clinical studies are needed to provide faster and safer protocols as well as to define optimal pretreatment medication regimens.

These 5 articles provide great impetus for the continued development of new desensitization protocols as the needs arise for new sensitizing medications to protect patients against hypersensitivity reactions and to permit increased quality of life and potentially longevity when there is no alternative medication.

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