Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

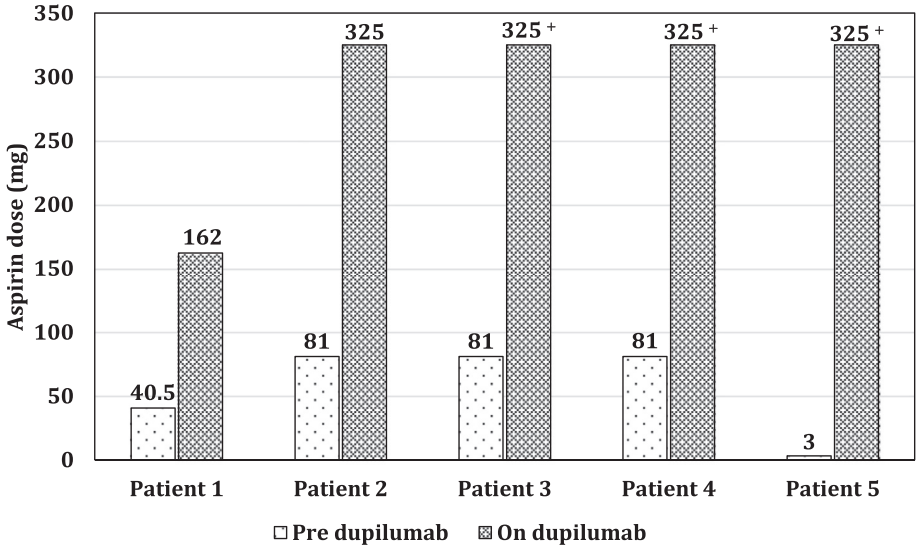

Figure 1. Aspirin threshold dose in aspirin-exacerbated respiratory disease before and during treatment with dupilumab.

mepolizumab.[9] The improvement in aspirin threshold is an additional consideration when selecting a therapeutic option for patients with AERD.

Despite this being a small case series, our data are the first to reveal that dupilumab may increase the aspirin threshold dose in patients with AERD, and even allow for ad lib use of nonselective COX inhibitors in these patients. Although larger studies are necessary to confirm these findings, we believe that there is significant use to perform an aspirin challenge while on dupilumab to determine the threshold dose of aspirin in patients with AERD, leading to the potential of ad lib use of nonselective COX inhibitors for analgesia and/or cardioprotection in patients with AERD.

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Drug desensitization in the coronavirus disease 2019 pandemic era

Local success to widespread potential

Along with the rise in the development and food and drug administration approval of novel drug therapies in the United States, an increasing number of allergic reactions to these new and targeted agents are occurring. These drugs include chemotherapeutics, monoclonal antibodies, and immunotherapies aimed at personalized treatment of a wide range of conditions from cancer and rheumatologic diseases to cystic fibrosis and diabetes.[1] Often, these reactions lead to use of second-line therapies that may place patients at risk of inferior treatment outcomes or increased adverse effects. The necessity to avoid a drug because of its potential allergic reaction upon re-exposure affects disease management, quality of life, and even potentially life expectancy in patients with cancer.[1] However, experience with the management of allergic drug reactions through protocols that permit patients to safely remain on first-line therapy despite an allergic reaction has grown in the past decade. Although initial drug desensitization practice was comprised of patients with cancer seeking help after experiencing hypersensitivity reactions (HSRs) to platinum agents,[2] allergy consultation practices have now been tasked with the evaluation of

Disclosures: The authors have no conflicts of interest to report.
Funding: Dr Blumenthal was supported by the National Institutes of Health K01AI125631 and the Massachusetts General Hospital Department of Medicine Transformative Scholars Program.
The content is solely the responsibility of the authors and does not necessarily represent the official view of the National Institutes of Health or the Massachusetts General Hospital.

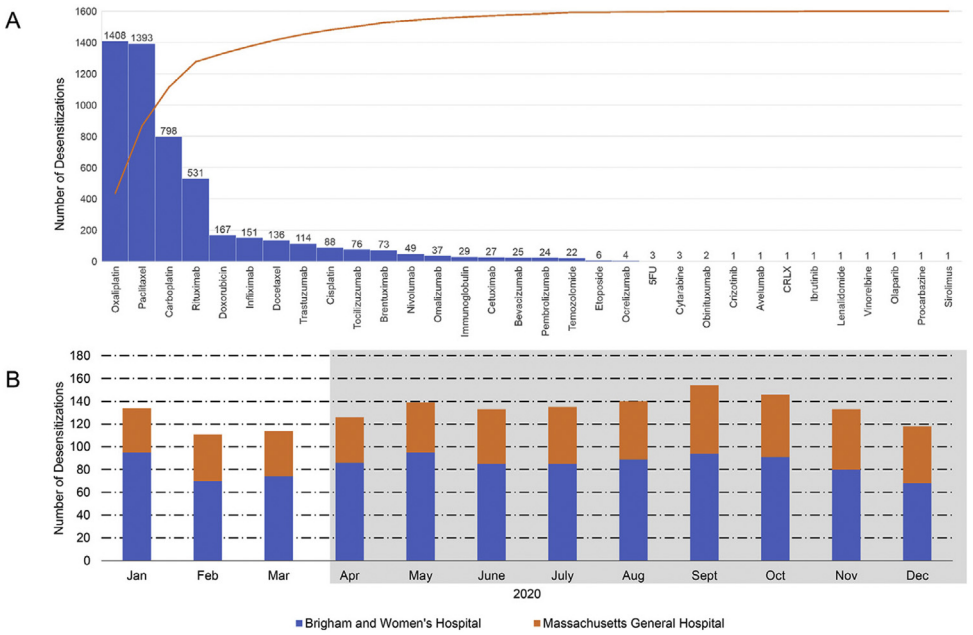

Figure 1. Drug desensitizations at 2 academic medical centers. A, 2015 to 2019. B, 2020. A, This pareto chart reveals the drug and drug type diversity across 5175 drug desensitizations performed including 3208 at Brigham and Women's Hospital and 1967 at Massachusetts General Hospital. B, This stacked bar chart reveals the 1583 drug desensitizations performed at Brigham and Women's Hospital (n = 1012) and Massachusetts General Hospital (n = 571) in 2020. The gray shading reveals consistent volume after the COVID-19 pandemic. COVID-19, coronavirus disease 2019.

patients who experience reactions that are endlessly diverse in terms of culprit drugs and potentially implicated mechanisms.

Although all drugs can cause adverse reactions, the subset of reactions that are immunologically mediated HSRs comprise approximately 20%. Immediate HSRs may be immunoglobulin E (IgE)–mediated HSRs with classic symptoms such as flushing, itching, palmar erythema, urticaria, angioedema, hypotension, and anaphylaxis; for some drugs, skin test positivity suggests possibility of an IgE-mediated mechanism. Previous exposure (for "priming") is often necessary for an IgE-mediated mechanism, but we recently learned of notable exceptions in which there are pre-existing antibodies (eg, cetuximab reactions) or environmental sensitizations (eg, taxane reactions) that permit IgE-mediated allergy to occur with the first dose.[3] However, some immediate HSRs may be non–IgE-mediated, potentially owing to direct activation of mast cells. For most HSRs that are immediate in onset and occur despite usual recommended premedication, desensitization can be safely and successfully used.

Desensitization, also termed an induction of tolerance procedure, is the gradual introduction of increasing amounts of a drug, leading to induction of temporary tolerance of that drug despite a previous allergic reaction. Reported more than 60 years ago, the first desensitization was to penicillin and became the prototype for modern desensitization protocols. Although immunologic activation may occur during desensitization, inhibitory mechanisms protect against anaphylaxis and most patients reach the therapeutic dose without harm.[1] In vitro models suggest that IgE desensitization is an antigen-specific process (ie, desensitization to a drug applies only to that specific drug) that blocks calcium flux, thereby affecting antigen or IgE or FcεRI complex internalization and preventing mast cell mediator release and HSR.[3] In vitro models support our clinical desensitization protocols that include the doubling of antigen doses, delivered with at least 10-minute intervals and starting at 1/1000 the target dose, to elicit inhibitory mechanisms preventing mast cell activation and blocking mediator release.[3] Desensitization also seems effective for HSRs that are not IgE-mediated, but the mechanism remains unclear.

With the assistance of standardized desensitization protocols, patients can continue to safely receive first-line drugs that are recommended for disease treatment. We and others have implemented thousands of desensitization protocols with success across diverse conditions and drug classes. Although the largest experience still lies with patients with gynecologic cancers and HSRs to the platin drugs carboplatin, cisplatin, and oxaliplatin, desensitizations have now been successfully performed to a myriad of agents, including taxanes (paclitaxel, docitaxel); doxorubicin; 5FU; irinotecan; monoclonal antibodies, such as rituximab, cetuximab, infliximab, trastuzumab, omalizumab, and crizotinib; even clinical trial drugs when permitted by the trial protocol (Fig 1A).

Implementation of desensitization protocols for malignancies and chronic inflammatory disease permits safe and on-schedule first-line treatments.[1,2,4] Drug desensitization is particularly important when the offending drug is the treatment of choice or the alternative drugs have a higher chance of treatment failure or unacceptable adverse effects. However, there is limited knowledge on the success of desensitization and switching to an alternative drug remains the most common choice when a patient experiences a HSR, in part because of lack of awareness of this procedure from other specialties and lack of access to allergy specialists to evaluate patients for desensitization.[1,5] Additional barriers to more widespread use of desensitization include lack of appropriate space and staffing for performing desensitization.

Although many areas of allergy and immunology clinical practices have been negatively affected by the coronavirus disease 2019 (COVID-19) pandemic, in our 2 Boston-based academic medical centers, drug desensitization has not (Fig 1B). Indeed, the total desensitizations in 2020 were greater than in many previous years and mean desensitizations were 120 monthly before COVID-19 onset and 136 monthly after COVID-19 onset. Furthermore, as the use of telehealth options including telemedicine and electronic

consults for drug allergy has expanded,[6,7] we envision new possibilities for patients who have HSRs to a first-line cancer or autoimmune disease therapy. Although patients used to drive for hours for an evaluation for desensitization, they can now be assessed virtually by a drug allergy specialist, although state regulations may limit some practices across state lines. More widespread access to desensitization will permit the establishment of specific collaboration efforts among allergists, consulting physician, and trained pharmacists.

Allergy specialist guidance and oversight, either in-person or virtual, is necessary for all desensitizations, because severe allergic outcomes have been described and management of HSRs during desensitization requires specific expertise. Drug desensitization should not be performed when equally effective alternative therapies are available. However, with more than 5000 published successful desensitizations with decades of safety data and no fatalities, and with telemedicine normalized into day-to-day practice, we envision that 2021 will be the year in which drug desensitizations can spread beyond the specialized academic medical centers. Physicians from specialties including oncology, gastroenterology, neurology, and rheumatology can refer patients for allergy assessment and potential desensitization after immediate reactions to drugs that represent a clear optimal treatment for their patient's condition. By partnering with allergists, these specialists can improve access to first-line treatments for cancer, vasculitis, and other severe chronic conditions by improving knowledge of, and access to, drug desensitization.

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