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Systemic reactions to inhalant immunotherapy using 1:1 target dosing

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ABSTRACT

Background: The 2007 immunotherapy practice parameters advocate maintenance dosing at 1:1 (1:20 maintenance concentrate). There is limited literature exploring the effect of 1:1 dosing on the rate of systemic reactions to subcutaneous immunotherapy (SRITs).

Objective: To investigate the effects of 1:1 dosing on SRITs in a large, academic practice.

Methods: We conducted a retrospective cohort study of all nonvenom and noncluster SRITs that occurred between 2005 and 2011. SRITs that occurred from August 2008 through December 2011, postparameter dosing (post-PD) was initiated, were compared to SRITs that occurred from January 2005 to July 2008 with preparameter dosing (pre-PD) using 1:50 as a maintenance concentrate.

Results: A total of 269 SRITs occurred in a 7-year period. Significantly more post-PD SRITs (131 of 38,548 injections) occurred than pre-PD SRITs (132 of 52,833 injections) (0.34% vs 0.25%, $P = .01$). However, when excluding 44 SRITs that occurred in established pre-PD patients transitioned to post-PD, there was no significant difference in SRIT rate (0.25% vs 0.22%), World Allergy Organization (WAO) grade, or SRIT time to onset. Nonred (non-1:1) vials accounted for a significantly larger proportion of all post-PD SRITs compared with all pre-PD SRITs (50.7% vs 31.1%, adjusted $P = .009$). Prior SRITs were reported less frequently among persons with post-PD SRITs (29.2% vs 70.8%, adjusted $P = .009$). In an adjusted logistic regression model, male sex (odds ratio, 7.9; 95% CI, 2.4–26) and longer time to reaction onset (odds ratio, 0.94; 95% CI, 0.89–0.99) were associated with higher WAO severity grade reactions.

Conclusion: Pre-PD vs post-PD SRIT rates were not significantly different, adjusting for patients transitioned from established pre-PD to post-PD. This finding suggests that post-PD is as safe as pre-PD. Male sex and faster time to reaction onset were associated with higher WAO grade reactions.

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Introduction

Allergen immunotherapy to inhalants is a widely recognized, efficacious treatment for both seasonal and perennial allergic rhinoconjunctivitis and allergen-triggered asthma.^{1–9} Before 2003, mixing standards and methods varied widely among practicing allergists.^{2–4} The 2003 practice parameters advocated the use of standardized microgram per milliliter of maintenance dose targets for selected allergens—*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*, mite, timothy grass, and cat—after research revealed that that a peak target dose resulted in superior relief compared with simple proportional mixing methods.⁵ In 2007, the Joint Taskforce on Practice Parameters updated the practice parameter on immunotherapy and advocated for a standardized and

stronger peak maintenance dosing at 1:1 (maintenance concentrate, without any added volume dilution to the manufacturer 1:20 bottle concentration).^{6,7,10–16} As practicing allergists have begun to adapt this more concentrated prescribing style during the past 5 years, there is limited literature exploring the effect of stronger dosing on the rate of systemic reactions to immunotherapy (SRITs) or comparing SRIT rates between more concentrate and more dilute dosing strategies, although ample data pertaining to rates of SRIT and their risk factors using non-1:1 dosing are available for comparison.^{3,17–30} Moreover, the effects of this change, including issues such as the relative safety of less dilute immunotherapy and its effects on the World Allergy Organization (WAO) severity grade of SRITs that occur with 1:1 dosing, are also poorly studied.³¹ We therefore describe the effects of the dosing change to the 2007 practice parameter–based dosing at a concentration of 1:1 in a large academic practice to determine whether there are differences in the number of SRITs, the effect on patients transitioned from one dosing method to the other, the comparative severity of the SRITs under older and newer dosing recommendations, the time of onset of SRITs

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Table 1

World Allergy Organization criteria for grading systemic reactions to immunotherapy

Grade	Cutaneous	Respiratory	Gastrointestinal	Cardiovascular	Other
1	Generalized pruritus, urticaria, flushing, or sensation of heat or warmth or angioedema (not laryngeal, tongue or uvular)	Rhinitis (eg, sneezing, rhinorrhea, nasal pruritus, and/or nasal congestion) or throat-clearing (itchy throat) or cough perceived to originate in the upper airway, not the lung, larynx, or trachea	Nausea		Conjunctival erythema, pruritus, or tearing; metallic taste; headache
2		Asthma: cough, wheezing, shortness of breath (eg, <40% PEF or FEV ₁ decrease, responding to an inhaled bronchodilator)	Abdominal cramps, vomiting, or diarrhea		Uterine cramps; sense of doom
3		Asthma (eg, 40% PEF or FEV ₁ decrease NOT responding to an inhaled bronchodilator or laryngeal, uvula, or tongue edema with or without stridor			Sense of doom
4		Respiratory failure with or without loss of consciousness		Hypotension with or without loss of consciousness	Sense of doom
5					Death

Abbreviations: FEV₁, forced expiratory volume in 1 second; PEF, peak expiratory flow.

after injection, and the associative factors that have influenced the occurrence of SRITs in our practice.

Methods

This study is a retrospective cohort study of the University of Michigan Division of Allergy and Clinical Immunology SRIT database. This database started in 2011 as part of a quality improvement project to track all SRITs for both venom and inhalant immunotherapy prescribed by and/or administered by the division's academic practice sites since 2005, according to current WAO grading criteria (Table 1).^{5,7,31} The database was queried to identify all nonvenom and noncluster SRITs that occurred between 2005 and 2011. Three authors (C.L.H., K.M.S., J.L.B.) reviewed all database cases for identification and reviewed the most recent immunotherapy order on electronic file before the date of the reported SRITs. A standardized datasheet was created for the purposes of this particular study, which contained the following information columns: dose style (concentrate; eg, 1:1 dosing or nonconcentrate); date of start of immunotherapy; transition of dosing style from proportional prescribing to 1:1; reaction date; age; sex; coadministration of angiotensin-converting enzyme inhibitor, β -blocker, or antihistamine; presence of asthma; the number of prior SRITs; time from injection to onset of symptoms of the SRITs; specific symptoms that comprised the SRITs; SRIT WAO grade; treatment of the SRITs; progression of the therapy (eg, maintenance vs building to maintenance); and vial color at time of SRITs.^{7,19,22,25,31}

All new immunotherapy prescriptions in the division ordered on or after August 1, 2008, were written using 1:1 maintenance concentrate.⁷ The concentration of the pre-August 2008 1:1 vial used by the practice before the initiation of a transition period beginning August 1, 2008, was calculated to be approximately 1:50 in the maintenance vial, but often the concentration varied substantially (Kiela Samuels, PharmD, and William Solomon, MD, personal communication, April 2007). Briefly, before August 1, 2008, all University of Michigan allergy practice clinicians wrote nonstandardized allergen extracts (wt/vol) at a concentration of 1:50 as the red (most concentrated) vial. This strength was calculated by using the manufacturer's extract of 1:20 and further diluting this to a final concentration of 1:50. This 1:50 vial then became the clinic maintenance

concentrate vial from which all serial dilutions were made (eg, green, blue, and yellow vials). Standardized cat at 10,000 BAU/mL was diluted to 1,000, 2,000, or 5,000 BAU/mL, and standardized grass at 100,000 BAU/mL was diluted to 20,000 BAU. Starting in July 2008, the practice formally discontinued this practice, standardized and non-standardized extracts were no longer diluted, and 1:20 and standardized extract was used as the maintenance concentrate. Between August 2008 and July 31, 2009, all existing immunotherapy patients were transitioned to 1:1 concentrate (1:20) at their next extract refill so that by July 2009, all patients receiving immunotherapy written by our practice would be formulated according to the recommendations for concentrate dosing and separation of high-protease containing items, specified in the 2007 practice parameter. Patients were transitioned using a volume $\times$ concentration formula ($m_1v_1 = m_2v_2$), and a dose comparison sheet was formulated to facilitate the process (eFig 1). Division policy has been to reduce a dose by 35% when extracts are refilled and fresh dilutions mixed. However, because transition also represented a significant increase in potency of the maintenance concentrate (1:50 to 1:20), the allergy physician had flexibility to reduce the dose beyond 35% for rebuilding (eg, a patient at 0.5 mL of red 1:50 could be transitioned to 0.35 of red 1:20 and rebuilt, reduced to a lower dose within red, or changed to a different color vial). No patient was transitioned without prior discussion with their attending physician, and patients were given the option to continue to take the less concentrated dose.

The following immunotherapy protocols for dosing and reaction assessment were used during the study period. The standard immunotherapy starting dose was the green vial, representing either a 1:50,000 or 1:20,000 concentration, with advancement as recommended per the 2003 and 2007 practice parameters toward a maintenance dose of 0.5 mL of the red vial, representing a 1:1 (vol/vol) concentration of either the maintenance concentrate at 1:50 or 1:20.

Individual antigen volumes for the red vial during the study period were per practice parameter recommendation for standardized allergens and variable for nonstandardized allergens.

The division used only 10-mL immunotherapy vials.

If diluent was added to the red vial to bring the final vial volume to 10 mL, it was still considered 1:1 (vol/vol).

When patients experienced SRITs, they were initially evaluated, assessed, and treated by an immunotherapy nurse, an allergy fellow

Table 2

Characteristics of the study population of individuals developing SRITs

Trend	No. (%)	Pre-PD immunotherapy, %	Post-PD immunotherapy, %	Adjusted post-PD immunotherapy, %	P Value (pre-PD vs post-PD)
Male sex	65 (25.7)	47.69	52.31	38	.62
Asthma	126 (46.9)	42.06	57.94	45.92	.053
Taking histamine ₁ antihistamine	76 (28.4)	28	72	63.79	<.001
Maintenance dose	84 (31.3)	57.14	42.86	30.43	.07
Red vial reaction	122 (45.3)	67.21	32.79	29.91	.003
Received epinephrine	187 (70.8)	56.15	43.85	31.82	.001
Prior SRITs	126 (46.8)	56.6	43.3	31.03	.02
Exercise before SRITs	15 (5.58)	26.67	73.33	63.64	.08

Abbreviations: post-PD, postparameter dosing; pre-PD, preparameter dosing; SRIT, systemic reaction to subcutaneous immunotherapy.

(if one is available at the particular office site), and an attending physician. These individuals were responsible for grading the reaction, although the final grade was ultimately decided by the attending physician.

All immunotherapy prescriptions were written on paper during the study period. Records of SRITs and immunotherapy reactions were kept electronically.

Patients were stratified into 3 groups for comparison: pre-parameter dosing (re-PD, representing pretransition dosing made from a concentrate vial of 1:50 as described above), postparameter dosing (post-PD, beginning immunotherapy on or after August 1, 2008, and using a concentrate vial at 1:20, as described above), and the transition group (established pre-PD individuals who experienced an SRIT within the first year of the dosing transition to post-PD between 2008 and 2009, representing the group originally undergoing subcutaneous immunotherapy at a concentrate dose of 1:50 that was changed to 1:20 to become compliant with the 2007 guidelines). All SRITs that occurred during the transition year (August 2008 through July 2009) were reviewed a second time by 2 authors (M.J.G., K.M.S.), and the last order on file before the SRIT was reviewed to ensure the reactions were properly stratified to their respective group.

Patient demographics, medication use, characteristics of the reaction, and SRITs that occurred from August 2008 to 2011 during the post-PD period were compared to SRITs that occurred from 2005 to July 2008 with pre-PD. An adjusted post-PD analysis was additionally created, removing the SRITs that occurred within the transition group to allow for comparisons of the aforementioned variables involving only “new” pre-PD and post-PD starts on their respective immunotherapy strengths.

Trends and proportional differences among the 3 groups were evaluated through frequency analysis and cross-tabulation with the χ^2 test or Fisher exact test. WAO severity was dichotomized (grade 1 or 2 vs grade 3 or higher) and modeled as an outcome variable using multiple logistic regression. In addition, the time (in minutes) from injection to onset of SRIT was modeled using a negative binomial regression, considering time (in minutes) as an overdispersed count variable. We were not able to develop a proportional hazards model given that the entire dataset was composed of individuals who attained the outcome (had a SRIT), and therefore no patient outcome was censored. An α of .05 was considered significant for all analyses. Predictor variables were prespecified and backwards stepwise selection was not used, given this was an exploratory, hypothesis-generating analysis. All analyses were performed with Stata IC, version 12 (StataCorp, College Station, Texas).

Results

During the 7-year review period, there were 269 SRITs identified among 91,383 injections, for a cumulative SRIT rate of 0.29%. During the study period, there were approximately 1,100 patients per year receiving immunotherapy. There were no grade 5 reactions

reported during this 7-year time span. The demographic and baseline characteristics of the study participants are detailed in Table 2. Significantly more SRITs occurred in the post-PD (131 per 38,548 injections) than pre-PD (132 per 52,833 injections) period (0.34% vs 0.25%, $P = .01$). However, when 44 SRITs that occurred in previously established pre-PD patients who were transitioned to post-PD during 2008 to 2009 (to comply with new division policy) were excluded from analysis, no significant differences were observed in the frequency of SRITs between the pre-PD or post-PD regimen (eg, transition-adjusted group comparing new immunotherapy initiation on pre-PD or post-PD) (132 per 52,833 injections vs 87 per 38,373 injections, 0.25% vs 0.22%, $P = .47$). Figure 1 illustrates the proportion of SRITs that occurred in red (eg, 1:1) vials vs nonred vials, noting a significant upward trend in the proportion of SRITs that occurred in nonred bottles in both adjusted and unadjusted post-PD groups compared with pre-PD groups (60.2% vs 31.1%, unadjusted $P < .0001$, 50.7% vs 31.1%, adjusted $P = .009$). Overall, 84 reactions occurred at maintenance (48 pre-PD, 5 transition, and 21 post-PD), with 56 of 84 (66.7%) of these reactions at maintenance occurring in the red vial (41 pre-PD, 2 transition, and 13 post-PD). Maintenance reactions represented 46.3% of the total red vial reactions. (Note that reactions occurred in the red vial while building to maintenance and in patients who were at maintenance at a lower [yellow] dilution). No statistically significant difference was found between the groups with a history of a prior SRIT in the unadjusted analysis (56.6% in the pre-PD group vs 43.4% in the post-PD group, $P = .06$), although when adjusting for reactions in the transition group, prior SRITs were reported less frequently among persons experiencing a post-PD SRIT (29.2% vs 70.8%, $P = .009$). Fewer post-PD than pre-PD SRITs were treated with epinephrine (42.8% vs 56.2%, unadjusted $P = .002$, and 31.8% vs 68.2%, adjusted for the transition group $P = .001$), although more persons reporting post-PD SRITs were taking histamine₁ antihistamines at the time of the reaction (28% vs 72%, unadjusted $P < .001$, and 36.2% vs 63.8%, adjusted for the transition group $P < .001$).

No significant difference was found in the proportion of grade 1, 2, 3, or 4 WAO reactions between the groups, in either the transition unadjusted or adjusted analysis, or when WAO reaction grade was dichotomized (grade 1 or 2 vs grade 3 or 4). Overall, grade 3 or 4 WAO reactions occurred in 5% of adjusted pre-PD reactions, 6% of adjusted post-PD reactions, 5% of unadjusted pre-PD reaction, and 9.5% of post-PD reactions. Moreover, no significant difference was found in the proportion of reactions that occurred within 15 minutes, 15 to 29 minutes, and more than 30 minutes after injection in either the transition unadjusted or adjusted analyses for pre-PD vs post-PD (Table 3). As well, no significant differences were found in the proportion of pre-PD vs post-PD SRITs that occurred while building to maintenance or while at maintenance dosing in either transition unadjusted or adjusted analysis.

Table 4 details factors that influenced higher-grade (grade 3–4) vs lower-grade (grade 1–2) WAO reactions. In a multiple adjusted logistic regression model, male sex (odds ratio, 7.9; 95% confidence

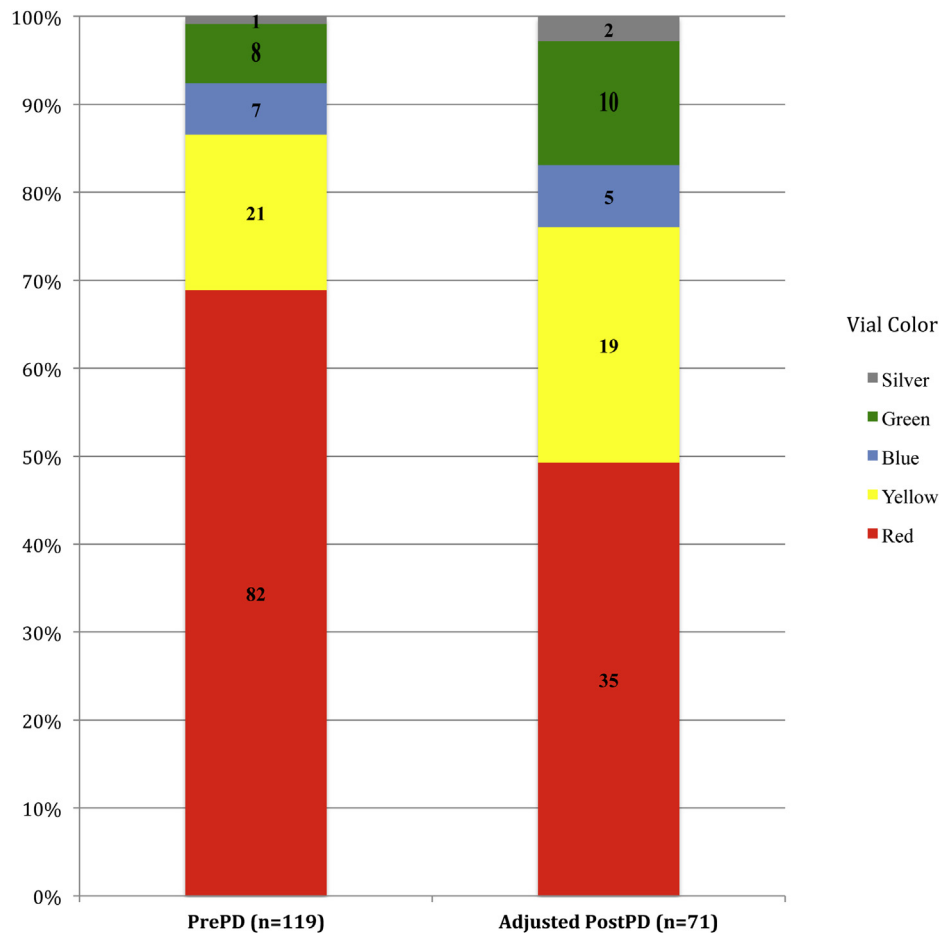


Figure 1. Proportion of systemic reactions to subcutaneous immunotherapy (SRITs) stratified by vial color at time of reaction by dosing regimen. Numbers within the column represent the total number of reactions at that respective dilution color.

interval, 2.4–26) was significantly associated with increased odds of a higher WAO grade reaction, and longer time to onset of SRIT (odds ratio, 0.94; 95% confidence interval, 0.89–0.99) was significantly associated with decreased odds of a higher WAO grade reaction. No significant association was noted between pre-PD, post-PD, or dosing transition to post-PD and the odds of experiencing a higher WAO grade SRIT. The amount of time (in minutes) to reaction onset was modeled as a count variable in a negative binomial regression as an additional study outcome (Table 5). Reactions that occurred at maintenance, grade 4 WAO reactions, persons 40 to 65 years old, and persons who received epinephrine had significantly lower adjusted incidence rate ratios of a SRIT, with a longer time to onset after injection (indicating a lower rate of occurrence for this

variable). Asthma was associated with a higher adjusted incidence rate ratio of a SRIT, with a longer time to onset after injection (indicating a higher rate of occurrence for this variable).

Discussion

This study comprehensively explores the safety of the Joint Taskforce on Practice Parameters 2007 recommendation to formulate more potent immunotherapy, using concentrate (1:1) dosing, compared with more dilute maintenance dosing previously used by our practice. Dosing at 1:1 in theory should deliver a more potent maintenance dose to help drive the immune response and produce a more beneficial response to therapy, which was a motivation

Table 3
Comparison of WAO SRIT grade and time to reaction onset by dosing method

Trend	No. (%)	Pre-PD immunotherapy, %	Post-PD immunotherapy, %	Adjusted post-PD immunotherapy, %
SRIT within 5 minutes	56 (21.9)	18.6	19.5	19.5
SRIT within 10 minutes	85 (33.2)	34.9	31.8	26.8
SRIT within 15 minutes	89 (33.5)	37.4	31	27.4
SRIT at 16–29 minutes	76 (28.5)	28.2	30.2	33.3
SRIT after >30 minutes	76 (38)	34.4	38.8	39.3
WAO grade 1 reaction	71 (27.7)	26.4	29.3	35.4
WAO grade 2 reaction	166 (64.8)	68.2	61.1	58.2
WAO grade 3 reaction	11 (4.3)	3.1	5.6	1.3
WAO grade 4 reaction	8 (3.1)	2.3	4	5.1
WAO grade 5 reaction	0	0	0	0

Abbreviations: SRIT, systemic reaction to subcutaneous immunotherapy; WAO, World Allergy Organization.

Table 4
Associations with a grade 3 or 4 WAO SRIT

Variable	OR (95% CI)	P value
Reaction time, min		
0–15 (reference)	1.00	
15–29	0.32 (0.09–1.23)	.10
≥30	0.14 (0.03–0.73)	.02
Patients taking H-1 antihistamine	1.62 (0.48–5.45)	.43
Prior SRIT	0.84 (0.45–1.53)	.56
At maintenance	0.54 (0.15–1.93)	.34
At red (highest) dilution strength	0.74 (0.21–2.61)	.64
Male sex	8.40 (2.57–27.49)	<.001
Age	1.02 (0.98–1.06)	.27
Immunotherapy		
Pre-PD (reference)	1.00	
Transition	2.19 (0.52–9.24)	.29
Post-PD	0.81 (0.2–3.32)	.77
Asthma	1.37 (0.42–4.41)	.60

Abbreviations: post-PD, postparameter dosing; pre-PD, preparameter dosing; SRIT, systemic reaction to subcutaneous immunotherapy; SRIT, systemic reaction to subcutaneous immunotherapy; WAO, World Allergy Organization.

behind the 2007 practice parameter recommendation.^{7,9} An additional motivation was to create a common dosing standard and reduce physician prescribing variation in immunotherapy dosing concentration.⁹ Our large academic practice was an example of such pre-PD inconsistencies.

In a large academic practice, spanning 91,383 immunotherapy injections during a 7-year period, we found no significant difference in the rate of SRITs that occurred with pre-PD vs post-PD, when adjusting for patients initially prescribed pre-PD and transitioned to post-PD. However, a significantly higher rate of SRITs was found in the post-PD group if the transition group (established patients receiving pre-PD immunotherapy who had their immunotherapy reformulated to post-PD in the midst of otherwise stable therapy to comply with our new divisional policy) was included in

Table 5
Associations with SRITs that have longer onset times^a

Variable	IRR ^a (95% CI)	P value
Patients taking histamine ₁ antihistamine	0.99 (0.77–1.28)	.96
Prior SRIT	0.94 (0.85–1.04)	.23
At maintenance	0.70 (0.54–0.92)	.009
At red (highest) dilution strength	0.99 (0.78–1.26)	.92
WAO reaction		
Grade 1 (reference)	1	
Grade 2	1.12 (0.86–1.45)	.39
Grade 3	0.64 (0.35–1.17)	.14
Grade 4	0.44 (0.22–0.9)	.02
Sex	0.88 (0.66–1.18)	.39
Age, y		
≤18	1	
19–39	0.72 (0.5–1.03)	.07
40–64	0.65 (0.45–0.95)	.03
≥65	0.72 (0.32–1.62)	.43
Immunotherapy dosing		
Pre-PD	1	
Transition	0.96 (0.69–1.34)	.82
Post-PD	0.87 (0.67–1.13)	.29
Asthma	1.28 (1.02–1.61)	.03
Epinephrine administered	0.38 (0.29–0.5)	<.001

Abbreviations: IRR, incidence rate ratio; post-PD, postparameter dosing; pre-PD, preparameter dosing; SRIT, systemic reaction to subcutaneous immunotherapy; SRIT, systemic reaction to subcutaneous immunotherapy; WAO, World Allergy Organization.

^aThe IRR represents the ratio of the event, trend, or variable presence occurring to not occurring per 1 minute of time that passed to the onset of a reaction. Ratios less than 1 represent a lower rate of occurrence during SRITs that developed with longer onset times, and ratios greater than 1 a higher rate of occurrence during SRITs that developed with longer onset times.

the analysis with those starting new post-PD immunotherapy. Moreover, no difference was found in the severity of the WAO grading for the SRITs between pre-PD and post-PD, both in the adjusted and unadjusted analysis. Interestingly, fewer adjusted post-PD SRITs were treated with epinephrine. Reasons for this specific finding require more study, given the strict guidelines that recommend this medication be used for SRITs.^{7,29,31,32} Strikingly, few other differences between the dosing groups were noted, with or without adjustment for the transitional group, which reinforces that 1:1 dosing is likely as safe as more dilute dosing that has been used previously. Significant differences were found in the proportion of SRITs that occurred in the red vial (eg, 1:1) vs nonred vials between pre-PD and post-PD, and proportionally fewer SRITs occurred in red vials vs other strengths with post-PD. The reasons for this are not entirely clear. However, we speculate this is mostly attributable to the fact that with stronger starting concentrations in post-PD immunotherapy the distribution of SRITs would be more evenly distributed among the 4 vial concentrations (Fig 1).

At a bivariate level we did not note higher post-PD rates (adjusted and unadjusted) of concurrent antihistamine use at the time of SRIT. It was beyond the scope of this study to determine motivation for concurrent antihistamine use. However, there is literature describing beneficial effects of antihistamine coadministration in preventing immunotherapy reactions.^{33–36} We did consider this as a potentially confounding factor, explaining no difference in transition-adjusted reaction rates, and included this as a variable in the regression models, but it was not noted to have a statistically significant association with reaction grade or faster time to reaction.

We observed that patients being transitioned from established pre-PD to post-PD were more vulnerable to SRITs. This therefore is an important subgroup to have identified because there may be more risk of SRITs in adjusting patients acclimated to more dilute immunotherapy compared with more concentrated immunotherapy. Overall, only 44 of more than 1,000 potentially transitioned patients had a SRIT. We have concerns about potential transition dosing variation within the conversions in eTable 1 as a factor in influencing transition reactions. However, it was beyond the scope of this study to explore what may be the underlying mechanisms or factors responsible for this vulnerability, and we are currently investigating this in a separate study. Other practices may wish to consider our experience and safety data before committing to transitioning patients already acclimated to more dilute therapy. Otherwise, this subgroup notwithstanding, within our population no significant differences were found in the rate of SRITs in patients starting new post-PD immunotherapy compared with pre-PD immunotherapy, which is strong evidence that concentrate-based dosing is well tolerated and safe.

Reaction severity and rapidity of onset were additional concerns of our investigation to provide a well-rounded assessment of 1:1 dosing safety. In adjusted regression models, we identified that male sex increased the odds for WAO grade 3 or 4 SRITs, and SRITs that occurred after 30 minutes decreased these odds. Moreover, we identified that WAO grade 4 SRITs, SRITs that required epinephrine treatment, SRITs that occurred at maintenance dosing, and SRITs in persons 40 to 65 years old were all significantly associated with more rapidly occurring reactions. Asthma was associated with more slowly occurring reactions. Collectively, this appears to validate that the 30-minute wait time after injection is likely appropriate, which was another significant change advocated in the 2007 practice parameter.⁷ However, we are aware that our data differ with prior reports, specifically in that we note different proportions of SRITs having a faster time of onset and relationship of SRITs to sex, asthma, and age.^{22,25,28–30} It is of note that these studies did not analyze post-PD immunotherapy, only pre-PD immunotherapy, and used different statistical analyses.

This study has several limitations. This was a single-center, observational, retrospective study. It was conducted at a large, tertiary referral center, with a dedicated monitoring system to observe and record SRITs, a clearly established and enforced protocol used in all of our offices and in a division that has a dedicated pharmacist with a PhD responsible for mixing all of the division extract orders. Moreover, there may be particular patient attributes among our allergic rhinoconjunctivitis and allergic asthma patients that we are unaware of or did not observe. This may include a predilection to initiate or withhold immunotherapy in certain types of patients. Such differences are difficult to measure, and altogether, these may decrease the generalizability of our findings to some degree outside centers similar to ours. Given that this was a hypothesis-generating study, there may be unmeasured variables of additional importance to explain the association between immunotherapy dose concentration and rate of SRIT that we did not consider beyond the several prespecified variables we believed were most crucial. As well, because this study was observational and not a randomized controlled trial, there cannot be any implications of causality. Lastly, our observational time frame for post-PD immunotherapy was only 3 years, which may not have been sufficient to fully observe the effects of post-PD immunotherapy, given that there were fewer injections provided overall in the post-PD period than in the pre-PD period. However, despite a difference of approximately 14,000 injections between the 2 periods, the number of injections in both periods was on the order of 3.8×10^5 and 5.2×10^5 , respectively, and provides sufficient power to discern even miniscule effect sizes.

Within a university population, we found convincing data that there was no difference in the rate of SRITs noted between patients receiving pre-PD vs post-PD immunotherapy, adjusted for exclusion of patients transitioned to post-PD from established pre-PD immunotherapy. This evidence is therefore strongly suggestive that 1:1 post-PD immunotherapy is as safe as pre-PD immunotherapy. Established pre-PD patients may be more vulnerable to an SRIT when transitioned to post-PD immunotherapy, a point for physicians to consider if they have not yet converted their practice to 1:1 dosing. We noted no significant differences in the WAO grade for the SRITs with post-PD compared with pre-PD immunotherapy, a higher proportion of nonred vial SRITs in post-PD patients, and significantly less treatment with epinephrine for post-PD SRITs. Further work is needed to better understand additional specific patient-associated factors that may influence reaction onset speed and severity, but these are important hypothesis-generating factors to consider.

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