

Increased risk of systemic reactions extends beyond completion of rush immunotherapy



Kevin A. Cook, MD, John M. Kelso, MD, and
Andrew A. White, MD

Clinical Implications

- This 1-year retrospective study found a peak in systemic reactions with the second injection after completion of the rush immunotherapy protocol. Premedication with the second injection after rush may be warranted.

TO THE EDITOR:

Allergen immunotherapy requires a build-up phase involving progressive dose increases with the goal of reaching a maintenance dose that promotes tolerance to encountered allergens. Conventional build-up protocols call for slow dose escalation over months. Accelerated protocols include cluster dosing with several escalating doses given on a single day, as well as rush schedules that utilize rapid dose escalation over 1 to 3 days. Accelerated build-up schedules reach maintenance dosing more quickly, and thus may achieve earlier therapeutic benefit.¹ However, aeroallergen immunotherapy administered by rush schedules results in more systemic reactions (SRs) compared with traditional and cluster schedules.² Proposed strategies to mitigate this increased risk have included selection of lower risk patients, lowering of the target dose to be reached, and use of premedication regimens. Premedication for rush immunotherapy often consists of a combination of antihistamines, oral corticosteroids, and/or leukotriene modifier drugs. Specific combinations have not been compared in head-to-head trials; however, rates of SRs are lower with premedication ranging from 7.2% to 27% versus 27% to 100% without premedication.^{3,4}

In our clinic, we offer a 1-day rush schedule with dose escalation to a target of 0.1 cc of 1:10 vol/vol dilution of a maintenance concentrate (Table I). Patients receive premedication with 10 mg cetirizine, 150 mg ranitidine, 10 mg montelukast, and 50 mg prednisone at least 1 hour before beginning the rush protocol. One week after rush patients continue immunotherapy build-up using a traditional dose escalation schedule beginning with a dose of 0.2 cc of 1:10. Soon after employing this protocol, we noted a number of SRs with the first weekly injection after rush. This empiric observation led us to also prescribe the same premedication with the first injection after rush. A similar approach has been described with a trend toward fewer SRs with the first injection after rush.⁵

To further query patterns of SRs with rush immunotherapy, we retrospectively reviewed allergen immunotherapy administration records related to all SRs in 4 outpatient clinics in San Diego County from October 1, 2015, to September 30, 2016. Shot records were analyzed to determine a build-up schedule (traditional, cluster, or rush), injection number after rush (if applicable), reaction severity classification, and treatment required.

A total of 885 patients received an estimated 19,323 injections over the 1-year study period. Of the 885 patients, 217 (25%) started immunotherapy during the study period, whereas the remainder had begun immunotherapy in prior years. Among all 885 patients, 80 SRs were recorded among 54 patients (0.4% per injection, 6.1% per patient/year). Of the 217 new patients, 72 (33%) underwent build-up by the rush protocol, whereas the remaining 145 (67%) underwent build-up by traditional or cluster dose escalation. Of the 72 new rush patients, 19 (26%) experienced an SR versus 18 (12%) of the 145 new non-rush patients ($P = .013$). Among all 885 patients, 222 had started immunotherapy by the rush protocol in the year of study or prior years. The rate of SRs was higher in rush patients than non-rush patients (9.9% vs 4.8% per patient/year, $P = .016$), and when analyzed for reactions to the concentrate vial (6.7% vs 2.9% per patient/year, $P = .017$). A total of 36 total SRs were recorded among 22 patients who had started immunotherapy by the rush protocol in the year of study or prior years; 3 (8.3%) occurred during the rush schedule, 3 (8.3%) with the first injection after rush, 9 (25%) with the second injection after rush, and 0-3 with injections 3-9 after rush ($P = .046$ second vs third injection, Figure 1). An additional 13 SRs occurred after rush when at or near maintenance dosing (>10 injections after rush).

Severity of reactions was also analyzed in relation to the number of injections after rush (Figure 1). Only 2 patients experienced a grade 2 reaction during rush, one of whom required treatment with epinephrine. All SRs with the first injection after rush were grade 1 and did not require treatment with epinephrine. Six patients experienced a grade 2 reaction with the second injection after rush, 4 of whom required treatment with epinephrine. One grade 3 and one grade 4 SR were recorded after rush immunotherapy, each occurring at or near maintenance dosing.

A bimodal distribution is apparent in the number and severity of SRs after rush immunotherapy. Few and mild SRs occurred during rush and with the first dose after rush. Of note, patients received premedication for each of these visits. However, only 10 mg cetirizine was given in preparation for the second injections after rush. This correlated with the first peak in incidence of SRs, many of which required treatment with epinephrine. A second peak in SRs occurred at or near maintenance (≥ 10 injections after rush). This may be due to the initial mode of dose escalation, a dose-dependent effect, and/or the cumulative risk of a reaction with additional injections given. Rush patients experienced a higher rate of SRs even on the concentrate vial when compared with non-rush patients.

These findings suggest that the risk of SRs with our rush protocol extends beyond the initial rush schedule to at least the second injection after rush, and perhaps to the concentrate vial. Premedication with the first injection after rush appears to have blunted the number and severity of SRs. In contrast, treatment with cetirizine only before the second injection after rush was associated with a greater number of SRs and need for treatment with epinephrine. The prolonged risk of SRs after rush may imply that rush results in incomplete development of tolerance to subsequent doses. To our knowledge, this is the first report of increased risk of SRs beyond the first injection after rush.

TABLE I. Rush immunotherapy protocol at our clinic

Time	Dilution (vol/vol dilution of maintenance concentrate)	Dose (cc)
Day 1: >60 min before rush—premedication with cetirizine 10 mg, ranitidine 150 mg, montelukast 10 mg, and prednisone 50 mg		
Day 1: 0 min	1:10,000	0.3
Day 1: 30 min	1:1,000	0.3
Day 1: 60 min	1:1,000	0.5
Day 1: 90 min	1:100	0.1
Day 1: 120 min	1:100	0.3
Day 1: 150 min	1:100	0.5
Day 1: 180 min	1:10	0.1
Wait 90 min before discharge		
Post-rush build-up schedule		
Week 2: >60 min before injection - Premedication with cetirizine 10 mg, ranitidine 150 mg, montelukast 10 mg and prednisone 50 mg		
Week 2: <i>first injection after rush</i>	1:10	0.2
Week 3+: Oral antihistamine before injection		
Week 3	1:10	0.3
Week 4	1:10	0.4
Week 5	Concentrate	0.05
Week 6	Concentrate	0.1
Week 7	Concentrate	0.15
Week 8	Concentrate	0.2
Week 9	Concentrate	0.25
Week 10	Concentrate	0.3
Week 11	Concentrate	0.35
Week 12	Concentrate	0.4
Week 13	Concentrate	0.45
Week 14	Concentrate	0.5

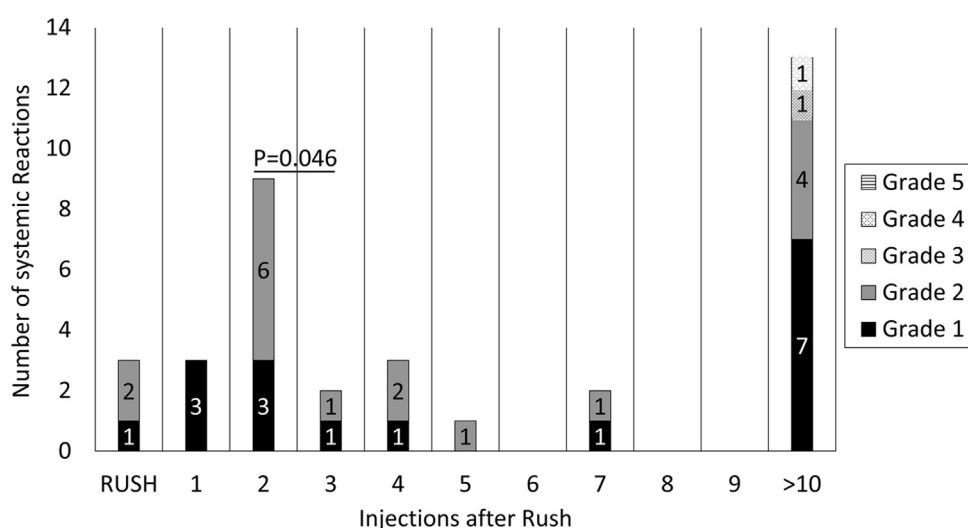


FIGURE 1. Systemic reactions after rush—reaction number and severity. Note: Determination of reaction severity utilized the World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System, with grade 1 indicating mild single organ system involvement, whereas grade 5 indicates a reaction resulting in death.⁶ Note: *P* value comparing systemic reactions recorded with second versus third injections after rush, calculated by Fisher's exact test.

There are no guidelines or recommendations regarding the use of premedication after completing a rush schedule.

Limitations of this study include its retrospective design. Confounding variables may exist between patients who elected to pursue a rush schedule versus those who did not. The study also lacks an intervention to address the apparent high rate of SRs after rush. The addition of premedication with the first injection after rush was started before the study period; thus the apparent efficacy of this approach is limited to empiric observation and comparison with rates of SRs with later injections. A randomized, placebo-controlled study of premedication with the first and second injections after rush would provide a higher degree of evidence for this approach.

In conclusion, this 1-year retrospective study found a peak in SRs with the second injection after the rush immunotherapy protocol. Premedication with the second injection after rush may be warranted.

Scripps Clinic, Division of Allergy, Asthma and Immunology, San Diego, Calif
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Corresponding author: Kevin A. Cook, MD, Scripps Clinic, Division of Allergy, Asthma and Immunology, 3811 Valley Centre Dr., S99, San Diego, CA 92130.
E-mail: cook.kevin@scrippshealth.org.

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