

Table 1

Average annual hospital admissions rates for allergic diseases in the United Kingdom from July 1, 2008 to June 30, 2011 by age group and gender per 100,000 population

	0–15 Years	16–75 Years	76+ Years
Allergic rhinitis and sinusitis (J30.1 to J30.4)			
Male	22.72	4.04	0.24
Female	9.63	5.92	0.30
Asthma (J45.0)			
Male	561.44	62.58	77.58
Female	55.15	147.09	151.20
IgE-mediated GI reactions (K52.2)			
Male	2.88	0.28	0.66
Female	1.34	0.43	1.18
Allergic urticaria (L50.0, L56.1)			
Male	7.85	0.82	0.66
Female	4.01	1.51	0.84
Anaphylaxis (T78.0 to T78.4, T80.5, T88.6)			
Male	33.92	8.86	9.91
Female	15.93	16.00	11.74
All causes			
Male	690.46	84.66	103.51
Female	96.79	181.21	184.43

Values are admissions per 100,000 person-years.

search.⁷ Still, the ethnicity data available were not sufficiently comprehensive to allow further exploration of ethnicity differences. Furthermore, the percentage of patients (J30.4) that underwent sinus surgery cannot be obtained. In conclusion, apparent geographic variations in hospital admissions for allergies were observed in recent years. More hospital admissions attributable to allergies were recorded in the more deprived areas. Because reducing hospital admissions continues to play an important role in

primary care, future prevention policy on reducing hospital admissions for allergy that is regionally specific for identifying and reducing over-utilization of health care costs should be considered.

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Ultrarush venom immunotherapy and the lipoxin a₄ inflammation resolution pathway

Venom immunotherapy (VIT) stimulates T_H1 cytokines and allergen-specific, interleukin 10 (IL-10)–producing, T-regulatory cells, thereby inducing tolerance.¹ We previously reported that intercellular adhesion molecule 1 is overexpressed in allergic patients and decreases after ultrarush VIT.² Thus, VIT can correct the imbalance in T-lymphocyte subpopulations and in IL-4 and tumor necrosis factor α production. Despite these achievements, the mechanisms of ultrarush VIT-induced tolerance remain incompletely understood.

Proinflammatory mediators are released during allergic reactions to Hymenoptera venoms, whereas the pivotal role of mediators that actively terminate inflammation is emerging.³ Among these, the lipoxins exert potent bioactions to stop inflammation and promote resolution.³ Lipoxin A₄ (LXA₄) reduces asthmatic bronchoconstriction and airway inflammation⁴ and stimulates IL-10 release.⁵ LXA₄ generation and LXA₄ receptor expression are reduced in asthmatic patients,⁶ supporting a role of LXA₄ in immunoallergic disorders.

To determine whether VIT is associated with changes in LXA₄ generation, we measured urinary immunoreactive LXA₄ (iLXA₄) in 13 patients (4 women and 9 men; mean [SD] age, 45.5 [14.0] years and 37.1 [8.7] years, respectively) undergoing ultrarush VIT. Hymnox (Roxall Italia, Rome, Italy), an aqueous preparation of *Vespula* species

or *Apis mellifera*, was administered subcutaneously to 13 patients, according to an established protocol.² At the end of the incremental phase, the cumulative dose, administered in 13 fractions every 15 minutes (3 hours), was 111.101 μ g. All patients received a maintenance dose of 100 μ g on day 15 and thereafter once a month for 24 months. Urine samples were collected at baseline and at the end of the incremental phase. iLXA₄ was measured according to a method developed in our laboratory.⁷ Ultrarush VIT efficacy was monitored over time by evaluating the systemic allergic reaction to unintentional Hymenoptera stings after ultrarush VIT compared with the systemic allergic reaction before ultrarush VIT.

iLXA₄ increased after ultrarush VIT (mean [SD], 0.0088 [0.003] vs 0.013 [0.006] ng/mg of creatinine; $P = .046$, Wilcoxon signed rank test). By stratifying patients for the specific IgE (sIgE) to total IgE (tIgE) ratio, which correlates with the clinical response to allergic-specific immunotherapy, we separated patients into 2 groups: group A, 7 patients with an sIgE/tIgE ratio less than 0.05; and group B, 6 patients with an sIgE/tIgE ratio greater 0.05. Basal iLXA₄ levels were higher in group A patients (mean [SD], 0.0103 [0.0022] vs 0.0071 [0.0033] ng/mg of creatinine; $P = .03$, Mann-Whitney test). All group B patients displayed a significant increase in urinary iLXA₄ after ultrarush VIT (mean [SD], 0.0071 [0.0033] vs 0.016 [0.0056] ng/mg of creatinine; $P = .03$, Wilcoxon test) (Fig 1). No significant changes were denoted in group A, although 3 patients had an increase in urinary iLXA₄ after ultrarush VIT (Fig 1). We observed an

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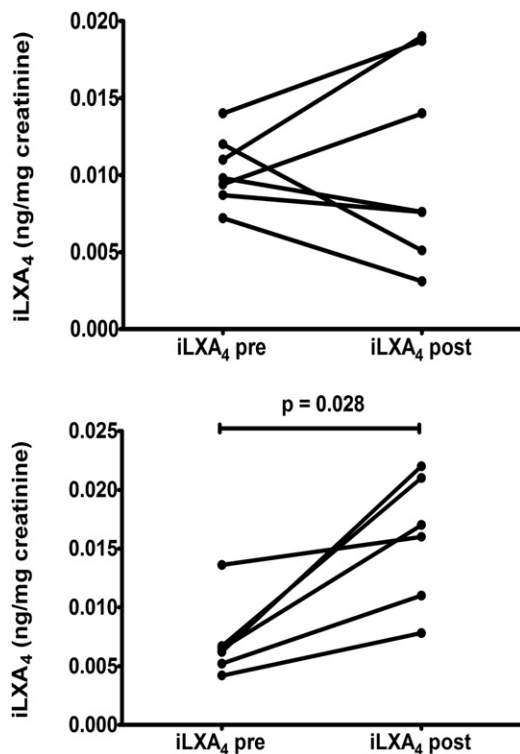


Fig. 1. Urinary immunoreactive lipoxin A₄ (iLXA₄) levels in 13 patients subjected to ultrarush venom immunotherapy. Urinary samples were collected at baseline and at the end of the ultrarush protocol. Top, Patients with a specific IgE (sIgE) to total IgE (tIgE) ratio less than 0.05. Bottom, Patients with an sIgE/tIgE ratio greater than 0.05.

inverse correlation between basal iLXA₄ levels and the systemic allergic reaction before ultrarush VIT ($\rho = -0.60$; $P = .03$, Spearman rank correlation test), which was stronger in group B ($\rho = -0.83$; $P = .04$, Spearman rank correlation test).

Results indicate that ultrarush VIT induces a rapid increase in iLXA₄. The source of ultrarush VIT-induced LXA₄ remains to be established, although melittin, a main fraction of bee venom proteins, stimulates neutrophil 5-lipoxygenase and platelet 12-lipoxygenase, 2 key enzymes of lipoxin biosynthesis.⁸ Consistent with this finding, iLXA₄ increased in 100% of patients who received *A mellifera*. VIT activation of additional lipoxin biosynthetic pathways (ie, epithelial cell leukocyte interactions)⁴ cannot, however, be excluded. By stratifying urinary iLXA₄ values for an sIgE/tIgE ratio cutoff of 0.05, we identified a subpopulation of 6 patients with an sIgE/tIgE ratio greater than 0.05 and reduced iLXA₄ levels. Compared with those with a lower sIgE/tIgE ratio, these patients had a higher negative correlation between iLXA₄ and systemic allergic reaction before ultrarush VIT and a significant increase in iLXA₄ after ultrarush VIT. Altogether, these results suggest that (1) higher sIgE/tIgE ratios may be predictive of more efficient ultrarush VIT-induced anti-inflammatory responses (ie, increase in LXA₄) and (2) higher basal iLXA₄ appears to be associated with less severe anaphylactic reactions to Hymenoptera venoms, thus confirming the protective role of LXA₄ in this setting.

Although we have no information regarding the mechanisms of the potential protective actions of LXA₄ in Hymenoptera venom triggered allergic reactions, it is noteworthy that LXA₄ induces the release of IL-10,⁴ which is considered a main mediator of ultrarush VIT-induced tolerance.

In conclusion, the present data uncover the involvement of LXA₄ in allergic reactions to Hymenoptera venoms. This represents a novel aspect of LXA₄ pathobiology, which may open new avenues for the understanding and treatment of these syndromes. Moreover, the finding that the group response is stratified into IgE ratios provides a potential basis to monitor individual responses to Hymenoptera venoms that could be useful in future studies with larger cohorts of patients: assayed biomarker of an individual's ability to resolve local allergic challenges.

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