Sublingual Immunotherapy: Where Does It Stand?

Esther Landhuis

July 07, 2021

This is part 3 of a three-part series. Part 1 is here. Part 2 is here.

Sublingual immunotherapy (SLIT) emerged over a century ago as a gentler alternative to allergy shots. It uses the same antigens found in allergy shots, delivering them through tablets or drops under the tongue rather than by injecting them into the skin.

Dr Sakina Bajowala

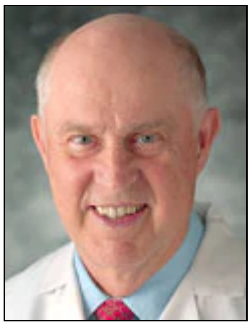
Yet injection immunotherapy has been the mainstay of allergy treatment in the United States. Allergy shots are "the bread and butter, keeping the lights on at allergy practices," said allergist Sakina Bajowala, MD, of Kaneland Allergy and Asthma Center, in the Chicago area. So even "when environmental SLIT showed quite clearly that it had efficacy, people were so slow to adapt."

SLIT — a daily treatment that builds protection from allergens gradually over years with few side effects — is popular around the globe, particularly for environmental allergies. But only a handful of clinics offer food SLIT. Even though recent trials in peanut-allergic children show that SLIT is far safer than oral immunotherapy and about as effective as the US Food and Drug Administration (FDA)–approved peanut allergy product and has lasting benefits for toddlers, many allergists lack experience with customized immunotherapies and hesitate to offer an unregulated treatment for which the evidence base is still emerging.

Why Hasn't Food Allergy SLIT Caught On?

One issue is that there is scant evidence from randomized controlled trials. The treatments that clinics offer often hinge on insurance coverage, and increasingly, insurers only cover FDA-approved products. FDA approval requires thousands of patients being enrolled in long, expensive studies to prove the treatment's merit. In a similar vein, doctors are trained to question methods that lack a strong publication base, for good reason.

Yet SLIT caught the attention of pioneering physicians who were intrigued by this "low and slow" immune-modifying approach, despite limited published evidence, and they sought real-world experience.



Dr David Morris

The late physician David Morris, MD, came across SLIT in the 1960s while searching for alternative ways to help mold-allergic farmers who were suffering terrible side effects from allergy shots. Morris attended conferences, learned more about sublingual

techniques, got board certified in allergy, and opened Allergy Associates of La Crosse, in Wisconsin, in 1970 to offer SLIT as a treatment for food and environmental allergies.

Dr Nikhila Schroeder

Morris and colleagues developed a protocol to create custom SLIT drops tailored to individual patients' clinical histories and allergy test results. The method has been used to treat more than 200,000 patients. It has been used by allergist Nikhila Schroeder, MD, MEng, who learned SLIT methods while treating nearly 1000 patients at Allergy Associates. In 2018, she opened her own direct-care SLIT practice, Allergenuity Health, in the Charlotte metropolitan area of North Carolina (see part 2 of this series).

Bajowala's clinic offers SLIT in addition to oral immunotherapy (OIT). She was encouraged by the recent toddler SLIT data but wondered whether it would translate to a real-world setting. According to her calculations, the published protocol — according to which participants receive up to 4 mg/d over 6 months and continue receiving a daily maintenance dose of 4 mg for 3 years — would cost $10,000 per patient.

With this dosing regimen, the intervention is unaffordable, Bajowala said. And "there's no way to make it cheaper because that's the raw materials cost. It does not include labor or bottles or profit at all. That's just $10,000 in peanut extract."

Owing to cost, Bajowala's clinic generally uses SLIT as a bridge to OIT. Her food allergy patients receive up to 1 mg/d and remain at that dose for a month or so before transitioning to OIT, "for which the supplies are orders of magnitude cheaper," she said.

Schroeder said there is evidence for efficacy at microgram and even nanogram dosing — much lower than used in the recent food SLIT trials. Maintenance doses range from 50 ng/d to 25 µg/d for environmental SLIT and 4–37 µg/d for food SLIT, she said. The La Crosse method uses even lower dose ranges.

However, dosing information is not readily available, Schroeder noted. She has spent years scrutinizing articles and compiling information from allergen extract suppliers — all the while treating hundreds of SLIT patients. "I have had to expend a lot of time and effort," said Schroeder. "It's really hard to explain quickly."

In the published literature, SLIT dosing recommendations vary widely. According to a 2007 analysis, environmental allergy symptoms improved with doses over a 1000-fold range. What's more, success did not scale with increased dosing and seemed to depend more on frequency and duration of treatment.

Dr Edwin Kim

There are fewer studies regarding food SLIT. The most promising data come from recent trials of peanut-allergic children led by Edwin Kim, MD, director of the UNC Food Allergy Initiative, University of North Carolina School of Medicine, Chapel Hill, North Carolina. Still, "I am nervous to tell people to go do this based on 150 kids at one site," Kim said. "We need to have a gigantic study across multiple sites that actually confirms what we have found in our single center."

Because there are few published trials of food SLIT, confusion about which doses are optimal, how early to start, and how long the benefits last will be a barrier for many clinicians, said Douglas Mack, MD, FRCPC, assistant clinical professor in pediatrics at

McMaster University, in Hamilton, Ontario, Canada.

Dr Douglas Mack

Much could be learned from Allergy Associates of La Crosse, Allergenuity Health, and other clinics with SLIT experience involving thousands of patients. But that real-world data are messy and difficult to publish. Plus, it is hard for private allergists to find time to review charts, analyze data, and draft papers alongside seeing patients and running a clinic — especially without students and interns, who typically assist with academic research, Schroeder said.

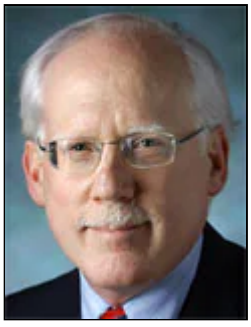
Ruchi Gupta, MD, MPH, professor of pediatrics and medicine at Northwestern University Feinberg School of Medicine, in Chicago, Illinois, and colleagues worked with a La Crosse team 6 or 7 years ago to try to analyze and publish SLIT outcomes for 121 peanut-allergic children who were treated for food and environmental allergies at the Wisconsin clinic. The researchers had hoped to publish an article describing caregiver-reported and clinical outcomes.

Among 73 caregivers who responded to a survey, more than half reported improved eczema, asthma, and environmental allergy symptoms, and virtually all families said SLIT calmed anxieties and minimized fear of allergic reactions. However, the clinical outcomes — skinprick test results, immune changes, and oral food challenges — were not as robust. And the data were incomplete. Some patients had traveled to La Crosse for SLIT drops but underwent skin and blood testing with their local allergist. Compiling records is "so much harder when you're not doing a prospective clinical trial," Gupta said.

Jeff Kessler, MBA

The caregiver-reported outcomes were presented as a poster at the 2015 annual meeting of the American College of Allergy, Asthma and Immunology and the 2016 annual meeting of the Pediatric Academic Society, said Jeff Kessler, MBA, FACHE, who is practice executive at La Crosse. However, with only self-reported data and no convincing lab metrics, the findings were never submitted for publication.

Others are eager to see clearer proof that SLIT works at doses lower than those published in the most recent trials. "If we can get efficacy with lower doses, that means we can increase accessibility, because we can lower the cost," Bajowala said.



Dr Robert Wood

Robert Wood, MD, professor of pediatrics and director of pediatric allergy and immunology at Johns Hopkins, has a pending grant proposal for a multifood trial of SLIT. "It's a big missing piece," he said.

Mack said that in Canada, there was "almost an instant change in group think" when the Canadian Society of Allergy and Clinical Immunology published guidelines in support of OIT. With the new guidelines, "people are less concerned about liability," Mack said. "Once they start getting into OIT, I think you're going to see SLIT coming right along for the ride."

The shift will be slower in the United States, which has 20 times as many practicing allergists as Canada. Nevertheless, "I totally think SLIT has a place at the table," Mack said. "I hope we start to see more high-quality data and people start to use it and experiment with it a bit and see how it works."

Sakina Bajowalahas consulted for Solid Starts, has a speaking/media contract with Novartis, and is part owner of Wise Prince, LLC, which develops digital tools to optimize the safety of food allergen desensitization.

Ruchi Gupta, reports relationships with Before Brands, Kaleo, Mylan, Thermo Fisher Scientific, Aimmune Therapeutic, the Stanford Sean N. Parker Center for Allergy Research, and the Denise and Dave Bunning and Sunshine Charitable Foundation.

Jeff Kessler is president and director of Allergychoices, a company that equips other doctors to provide sublingual immunotherapy.

Edwin Kim reports consultancy with Aimmune Therapeutics, Allako, AllerGenis, Belhaven Pharma, DBV Technologies, Duke Clinical Research Institute, and Nutricia; advisory board membership with ALK, DBV Technologies, Kenota Health, and Ukko; grant support from the NIH's National Institute of Allergy and Infectious Diseases, National Center for Complementary and Integrative Health and Immune Tolerance Network; Food Allergy Research and Education, and the Wallace Research Foundation.

Douglas Mack is a principal investigator for DBV and ALK and has consulted or spoken for ALK, Aimmune Therapeutics, Bausch Health, Kaleo, Medexus, and Pfizer.

Robert Wood receives research funding from NIH, Astellas, Aimmune, DBV, HAL-Allergy, Sanofi, Genentech, Regeneron, and Food Allergy Research and Education.

Nikhila Schroeder has disclosed no relevant financial relationships.

This is part 3 of a three-part series. Part 1 is here. Part 2 is here.

Esther Landhuis is a freelance science journalist in the San Francisco Bay Area. Her work has appeared in Scientific American, Nature, Kaiser Health News, Undark, and elsewhere. She can found on Twitter @elandhuis.

For more news, follow Medscape on Facebook, Twitter, Instagram, and YouTube.

Send news tips to news@medscape.net.

Cite this: Sublingual Immunotherapy: Where Does It Stand? - *Medscape* - Jul 07, 2021.