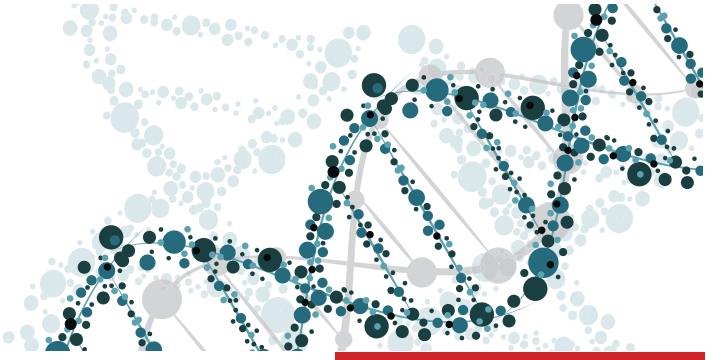
RGA

Global Health Brief



Issue 12, November 2019

# Navigating Allergen-Specific Immunotherapy (AIT)

Allergy-related diseases have existed for millennia but since 1960 have experienced an abnormally large increase in incidence. Asthma and food allergies in particular are at epidemic numbers, with as much as 30% of the world's population now afflicted. This has caused some to label allergies "the epidemic of the 21st century." Indeed, allergies are currently the sixth leading cause of chronic illness in the U.S. alone, with annual costs as of 2018 exceeding US$18 billion.

Allergen-specific immunotherapies (AITs), which offer relief for some classes of allergies, are increasingly becoming a preferred treatment option. However, these treatments can be challenging to review and assess from the insurance perspective. This brief offers helpful guidance.

Sincerely,
Dr. Dipta Rai
Associate Director, Health Claims Management, Malaysia
RGA

## What is an Allergy?

An allergy, simply put, is the immune system's overreaction to common substances in the environment which are harmless to most. These substances, known as allergens, include dust mites, pet dander, pollens and molds, ticks, chemicals (e.g., air fresheners, perfumes), particulate matter, latex, certain foods, and medications such as penicillin.

The genetic tendency to develop allergies is called "atopy." When atopic individuals are exposed to allergens, an immune reaction occurs that leads to allergic inflammation. Reactions can include allergic rhinitis (hay fever), allergic conjunctivitis (affecting the nose and eyes), eczema (atopic dermatitis), urticaria (hives and itching), breathing difficulties (including allergic asthma), and in some cases, anaphylaxis and even death.

## Treatment Modalities

Currently, three treatment modalities exist for allergies: allergen avoidance or minimization; pharmacotherapy (medications); and allergen-specific immunotherapy (AIT).

Allergen avoidance or minimization relies on identifying the cause of the allergy (i.e., the allergen) and taking steps to reduce the patient's exposure to it. For example, reducing dust in the home may help lessen symptoms for individuals allergic to dust mites.

Pharmacotherapy, or symptomatic treatment, relies on several types of medications, both prescription and over-the-counter. These include:

- Antihistamines, which reduce symptoms by blocking the release of histamine from mast cells. Antihistamines are available in pill form as well as nasal and eye sprays
- Intranasal corticosteroid nasal sprays (INCS), which can effectively treat moderate to severe allergic rhinitis
- Mast cell stabilizers, available as eye drops or nasal sprays, which aim to prevent the body from releasing histamine and can help with itchy, watery eyes or an itchy, runny nose
- Decongestants, which provide short-term relief for nasal stuffiness by shrinking swollen blood vessels in the nose
- Topical corticosteroid creams and ointments, which can relieve skin itchiness and stop allergic rashes from spreading
- Oral corticosteroids, generally only available by prescription, which may reduce allergic swelling and stop severe reactions
- Adrenaline (epinephrine), emergency first aid for anaphylaxis, a severe and life-threatening allergic reaction, which comes in pre-measured and self-injectable devices, and must be administered within minutes of the first sign of an anaphylactic reaction

For certain conditions, such as moderate to severe allergic rhinitis, therapies that combine two or more of the above are sometimes recommended for improved efficacy.

The rest of this brief will focus on AIT – the third treatment option.

## About AIT

AIT is defined as the repeated administration of regular and gradually increasing doses of extracts of specific allergens to patients with IgE-mediated conditions. Its aim is to induce a tolerance of natural exposure to the causative allergen(s) and achieve long-term response remission. Essentially, AIT works very much like a vaccine: The body responds to the controlled amounts of a particular allergen given in gradually increasing doses by developing an immunity to or tolerance of that allergen. This modality has successfully desensitized individuals suffering from allergic rhinitis, allergic (but not chronic) asthma, and venom and drug allergies.

The ability of AIT to modify the natural course of an established allergic disease is unique among non-communicable diseases. It has been used to treat allergic diseases for more than a century, and is the only treatment modality that addresses an underlying allergy's dysfunctional immune response rather than simply treating or suppressing symptoms. The most current research is focusing on AIT's potential applicability for certain food allergies and for atopic dermatitis.

AIT's safety and efficacy has been documented in several systematic reviews. It reduces symptoms and the need for medication to manage these symptoms and improves quality of life for allergy sufferers. Furthermore, the effect can continue for years after discontinuation of treatment. However, evidence regarding its cost-effectiveness is limited.

## Types of AITs

AIT can be administered in two ways: either as subcutaneous immunotherapy (SCIT), more commonly known as allergy shots; or as sublingual immunotherapy (SLIT), consisting of drops or tablets given under the tongue.

There are two phases to the AIT process:

- Buildup: This involves receiving either injections or sublingual doses of the allergen. Dosing for SCIT is about one to three times per week, and for SLIT, a minimum of thrice weekly or as frequent as daily. Concentrations increase with each dose. The length of this phase depends on how the patient responds to the therapy and how long it takes to reach the effective dose (the dose at which the allergic reaction is reliably halted), but generally ranges from three to six months.

- Maintenance: This phase begins once the effective dose is reached. The maintenance phase dose depends on the patient's sensitivity to the allergen being treated and their response to the buildup phase. During maintenance, more time can elapse between doses, ranging anywhere from two to eight weeks. Frequency of the maintenance phase dose will be determined by the patient's allergist or immunologist.

Treatment is generally administered by trained personnel in doctor's offices, clinics, or day centers. Patients may note a decrease in allergen-related symptoms during the build-up phase, but it may take as long as 12 months after maintenance commences to notice real improvement. If the AIT regimen is successful, maintenance generally continues for three to five years.

Treatment facilities can manage occurrences of adverse effects, which are rare for both SCIT and SLIT. Both can cause local and/or systemic reactions. Swelling and redness at the injection site in SCIT and oral itching and tingling in SLIT are the most common local effects. In SCIT, mild to moderate systemic reactions occur in approximately 0.1% of recipients, while severe reactions are rare (one in every one million injections). However, SCIT should not be given to those with poorly controlled asthma or significant cardiovascular disease as the risk of adverse reaction is higher. With SLIT, systemic reactions are extremely rare.

An interesting aspect of AIT is that, although the exact mechanisms by which this occurs are unclear, inflammatory mast cells, basophils, and eosinophils become progressively unresponsive to allergens after AIT. This may be due to the therapy's induction of regulatory T cells, which inhibit reaction-promoting T-helper 2 cells. In addition, IgG4, an anti-inflammatory antibody produced by B cells, inhibits IgE-mediated hypersensitivity by binding to allergens, thus acting as blocking antibodies.

## Indications

AITs can be safely recommended to treat the following IgE-mediated allergies for patients whose hypersensitivity to allergens cannot be managed by medication or allergen avoidance:

- Allergic (extrinsic) asthma
- Dust mites
- Atopic dermatitis
- Hymenoptera-sensitive individuals (allergic to stings of bees, hornets, wasps, fire ants)
- Allergic rhinitis (caused by pollen or mold)
- Perennial rhinitis (chronic allergic rhinitis persisting year-round)
- Allergic conjunctivitis

There is also some evidence that AIT might be effective in the treatment of patients with aeroallergen sensitivities, and might prevent the development of allergic asthma in subjects with allergic rhinitis. Before offering this treatment, however, a patient with suspected allergic rhinitis, allergic conjunctivitis, or an allergy to insect sting venom should undergo a complete medical evaluation, including a detailed history, an appropriate physical examination, and selected laboratory tests.

A definitive diagnosis of allergic sensitivity depends on the results of allergy testing (immediate hypersensitivity skin tests or in vitro tests for serum-specific IgE). AIT should only be considered when positive test results for specific IgE antibodies correlate with suspected triggers and patient exposure.

AIT should not be given to patients who test negative for specific IgE antibodies related to their allergic reaction, or who test positive for IgE antibodies that do not correlate with their suspected triggers, clinical symptoms, or exposure. This means that the presence of specific IgE antibodies alone does not necessarily indicate clinical sensitivity. There is no evidence from well-designed studies that AIT for any allergen is effective in the absence of specific IgE antibodies.

This treatment can be administered to children and adults, although it is not typically recommended for children under age five. This is mostly due to the difficulties younger children may have in cooperating with the program and in articulating any adverse symptoms they may be experiencing.

## Costs

As mentioned, the overall cost effectiveness of AIT versus pharmacotherapy is difficult to determine. The many evidence-based examples of the long-term benefits of AIT for suitable patients are promising, which could justify the initial high costs of treatment versus long-term dependence on pharmacotherapy.

Several U.S.-based studies suggest that SCIT is associated with substantial healthcare cost savings, with an up to 80% reduction in costs seen three years after completion of treatment.

Current costs for SCIT are generally less than for SLIT. Seasonal allergies can be treated for half the year, but year-round allergies (e.g., dust mites) require continual treatment and hence costs can be double. Still, a recent study in Sweden noted that a cost savings of €6,800 over three years can be expected from treating house dust mite (HDM) allergy with SLIT in tablet form compared to SCIT. This includes costs for treatment, healthcare visits, travel, and lost productivity. The reduced number of healthcare visits compensates for the higher initial medication costs.

## Underwriting and Claims Considerations

From an underwriting perspective, it should be highlighted that AIT is not considered a cure for all allergic diseases. Some studies have shown symptom improvement as well as reduced incidence of hospitalization, but the data is still insufficient to show its absolute efficacy over longer periods.

AIT can be considered a medically necessary treatment option for individuals who fulfill the clinical criteria for eligibility.

In terms of claims, there are several matters to consider:

- Whether AIT is to be considered a prophylactic or preventive form of treatment, which is dependent on policy benefit wordings
- Whether treatment is done on an outpatient or day center basis, as the modality could conflict with some policy benefits
- The monetary limits for certain employee benefit outpatient plans
- Whether a policy's post-hospitalization benefits limits the duration for AIT recommended during a related inpatient episode

## In Conclusion

AITs do fulfill the fundamental criteria, both clinically and for claims, for "medically necessary," as it should be provided to the insureds who meet the clinical criteria for treatment. AIT is also clinically appropriate in terms of administration and effectiveness, and its overall costs over the long term could be negligible compared to other forms of treatment. Still, AIT poses a potential risk of being overused, and has the potential for claims abuse, since most are unaware of its clinical criteria for use or that it can be safely administered in an outpatient setting. However, this can be mediated with health policy benefits that limit its use and the duration of the course of treatment. It is important to weigh all aspects before making determinations on claims eligibility. ■