Allergen Immunotherapy in the Era of SARS-CoV-2

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Despite the challenges presented by the SARS-CoV-2 pandemic, many patients worldwide continue to require treatment for seasonal allergies and asthma. We outline the potential benefits of allergen immunotherapy (AIT) and consider strategies for treatment when health services are disrupted.

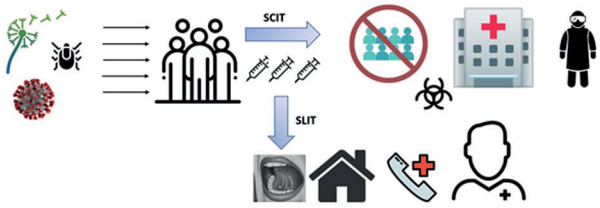
AIT consists of administering progressive doses of the substance causing allergic symptoms. Administration is repeated systematically at regular intervals, eliciting specific mechanisms that modulate a protective response of the immune system [1,2]. Several metanalyses of controlled studies have concluded that AIT is potentially effective for respiratory allergy, by improving symptoms and use of reliever and controller medications [1,3]. Some authors report reduced bronchial inflammation and enhanced lung function [4]. AIT is not recommended as a stand-alone treatment for asthma but may have an adjuvant effect in preserving clinical control of certain forms of the disease [5].

The World Health Organization and the Centers for Disease Control and Prevention stated that chronic lung diseases are high-risk conditions in the case of infection by SARS-CoV-2 (COVID-19), together with hypertension, heart disease, and diabetes. Subsequent research found the incidence of asthma in COVID-19 patients to be surprisingly low and not associated with the risk of acute respiratory distress syndrome [6,7]. Currently, there is no evidence of increased infection rates in people with asthma or induction of asthma exacerbations in COVID-19 patients, as observed for seasonal versions of coronaviruses. However, since asthma is associated with airway hyperreactivity to direct and indirect stimuli, the onset of an asthma attack subsequent to infection does not seem to be a remote possibility in uncontrolled disease and could worsen the patient's clinical status. Since insufficient control leads to a worse response to triggers, people with asthma are advised to continue taking their controller medications, including AIT.

AIT is commonly interrupted in cases of intercurrent infections until these have resolved [1]. The binding receptor of SARS-CoV-2 has been identified in angiotensin-converting enzyme (ACE) 2, and a T_H1 cytokine storm (IL-6 and TNF-α) sustains inflammation induced by COVID-19 in the lungs; therefore, a direct protective effect of AIT is not expected. We can speculate that the predominant T_H2 immune response in allergic patients might be beneficial and counter the inflammation process induced by SARS-CoV-2 [6]. Conversely, available therapeutic weapons against a T_H2 response, including AIT, could work indirectly by contributing to restore an impaired broad antiviral response. In fact, the allergic flare downregulates the defensive epithelial response and induces a suboptimal reaction of tissues to infection owing to delayed and decreased production of interferons. Moreover, even subliminal allergic inflammation enhances the expression of surface receptors working as binding sites for rhinoviral particles (ICAM-1), and common viral infections promote local release of proinflammatory cytokines (IL-25, IL-33), with consequent loop amplification of the T_H2 response leading to unstable disease and insufficient asthma control [8,9].

For years, AIT has mainly been administered subcutaneously (SCIT), with periodic injections in a continuous schedule over the year or clustered preseasonal approaches. SCIT is safe provided adequate precautions are taken in a supervised facility, with properly trained staff and equipment to manage severe reactions immediately. This approach requires patients to attend clinics for their weekly or monthly inoculations and may represent a critical issue in the era of SARS-CoV-2. Extraordinary governmental restriction orders were recently introduced by several national authorities to limit patients' flow to local hospitals and private medical services in order to manage the outbreak of the virus by restricting its spread. SCIT courses may therefore be delayed or interrupted. Some scientific societies have suggested general measures where possible, such as deferred commencement, extension of the interval between doses, and discontinuation in vulnerable people. These solutions remain a challenge for allergologists diverted to intensive care units and for centers where allergy units are temporarily closed (https://www.bsaci.org/announcements/modifications-for-adult-allergy-services-during-covid-19-pandemic).

Sublingual immunotherapy (SLIT) has become increasingly used in the last 2 decades as a valuable alternative to injections. Based on similar mechanisms of action, SLIT aims to induce local tolerance through stimulation of the oromucosal and gastrointestinal immune system and is nowadays supported by robust evidence of efficacy [2,3,10]. Nonetheless, not all patients benefit equally, and predictive biomarkers of response are still under investigation to enable identification of the best candidates. In order to ensure effectiveness, it is necessary to use purified standardized high-quality extracts, which—unfortunately—are not available for all allergens, and perform a proper diagnostic work-up. SLIT has the advantage of being self-administered, although recent high-dose native allergen tablets may require the first dose to be administered in the office to ensure appropriate management of initial local symptoms and reassure the patient [1]. The risk of severe reactions, including anaphylaxis, observed in some clinical trials appears remote and counterbalanced by the opportunity to ensure disease control in the delicate current scenario [11]. Moreover, SLIT is already an option in patients who have experienced systemic reactions after injections, and patients already tolerating SCIT are expected to have developed sufficient tolerance against the culprit allergen that would suggest a seamless transition to SLIT. Finally, alternative formulations with no history of anaphylactic reactions are available. These consist of chemically modified extracts (allergoids), and their use is well-established, with evidence of immunological anti-inflammatory action and clinical benefit [12,13]. In addition, for some SLIT preparations with a good safety profile, the build-up phase can be skipped to facilitate independent management of therapy by patients at home [14].



Preparation:	Tablets, drops, predosed dispenser, monodose vial
Build-up:	3-4 days, 4-6 days, 10 days
Maintenance:	Once a week, alternate days, daily
Regimen:	Pre-seasonal, pre–coseasonal, continuous
Switch to SLIT:	Permanent, temporary

Figure. SLIT as an alternative option to SCIT for patients with restrictions on reaching their doctors or allergy units in the COVID-19 era. SLIT indicates sublingual immunotherapy; SCIT, subcutaneous immunotherapy.

In this problematic setting, permanent or temporary switching of SCIT courses to SLIT may provide an option to overcome logistic restrictions and prevent the consequences of discontinuation. Previous experiences have confirmed the success of this approach [15]. Finally, this kind of telemedicine and remote monitoring obviates the need for patients to access hospital sites, with the attendant risks and reduced or redirected services (Figure).

In conclusion, allergy patients still require optimal treatment, even in the era of SARS-CoV-2. It is beneficial for asthmatic patients to avoid treatment discontinuation and reach or maintain an optimal degree of disease control in order to reduce the risk of exacerbation. Preserving the availability of all therapeutic tools in use, including AIT, is a priority for allergic patients during the pandemic. SLIT may represent an alternative option for all those patients unable to reach the medical setting to receive SCIT injections, and sublingual allergoids provide a safe and easy solution for management.

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Conflicts of Interest

Dr Compalati reports financial relationships with Lofarma S.p.A. outside the submitted work.

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