Allergen Immunotherapy in the era of SARS-CoV-2

Compalati E[1], Erlewyn-Lajeunesse M[2], Ali FR[3], Ojeda Fernández P[4], Garcia Nuñez I[5], Frati F[1], Mistrello G[1]

[1]Lofarma Scientific Department, Lofarma S.p.A., Milan

[2]Paediatric Allergy & Immunology, Southampton Children's Hospital, UK

[3]Barts Health NHS Trust, London, UK

[4]Clínica de Asma y Alergia Dres. Ojeda, Madrid, Spain

[5]Hospital Quirónsalud, Córdoba y Campo de Gibraltar, Spain

Corresponding author:

Enrico Compalati

Medical Dept. LOFARMA S.p.A.

Viale Cassala 40, 20143, Milano, Italy.

Email: enrico.compalati@lofarma.it

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Despite the challenges of the SARS-CoV-2 pandemic, seasonal allergies and asthma require ongoing treatment for a large proportion of patients worldwide. This commentary outlines the potential benefits of allergen immunotherapy (AIT) and considers strategies for treatment when health services are disrupted.

AIT consists of administering progressive doses of a substance causing allergic symptoms, to be 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 usage of reliever and controller medications [1, 3]. Some studies documented the reduction of bronchial inflammation and enhancement of lung function [4]. AIT is not recommend as a stand-alone treatment for asthma, but may have an adjuvant effect in preserving clinical control of certain forms of disease [5].

The World Health Organization and the Centers for Disease Control and Prevention stated that chronic pneumopathies represent conditions at high risk in case of infection by SARS-CoV-2 (COVID-19), together with hypertension, heart diseases, diabetes. Subsequent research found the incidence of asthma in COVID-19 patients was surprisingly low and not associated with the risk of

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ARDS development [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, asthma is associated with airways hyperreactivity to direct and indirect stimuli, therefore the onset of an asthma attack subsequent to infection seems not a remote possibility in uncontrolled disease and could deteriorate the overall clinical scenario. Since an insufficient control conditions a worse response to all triggers, people with asthma are advised to continue taking their controller medications, including AIT.

AIT is commonly interrupted in case of intercurrent infections until their resolution [1]. The binding receptor of SARS-CoV-2 has been identified in the angiotensin converting enzyme (ACE)-2 and a Th-1 cytokine storm (IL-6 and TNF-α) sustains the lung inflammation of COVID-19, thus it is not expected a direct protective effect of AIT. Speculatively, the predominant Th-2 immune response in allergic patients might be beneficial and counter the inflammation process induced by SARS-CoV-2 [6]. Conversely, the therapeutic weapons fighting a Th-2 response, including AIT, could work indirectly by contributing to restore an impaired broad antiviral response. In fact, the allergic flare down-regulates the defensive epithelial response and induces a suboptimal reaction of tissues to infections, due to a delayed and decreased production of interferons. Moreover, even subliminal allergic inflammation enhances the expression of surface receptors working as binding sites for rhino-viral particles (ICAM-1) and common viral infections promote the local release of pro-inflammatory cytokines (IL-25, IL-33) with consequent loop amplification of the Th-2 response in favor an unstable disease and insufficient asthma control [8, 9].

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AIT for years has been predominantly administered subcutaneously (SCIT), with periodic injections in a continuous schedule along 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 immediately manage severe reactions. This contemplates patients receiving SCIT moving regularly to clinics for their planned weekly or monthly inoculations, and may represent a critical issue in the era of SARS-CoV-2. Governmental extraordinary restriction orders were recently introduced by several national authorities to limit patients' flow to local hospitals and private medical services, in order to face the outbreak of the virus by restricting the risk of interhuman diffusion. The continuity of SCIT courses may therefore result delayed or interrupted. Some scientific societies suggested general measures where possible, as the deferred commencement, the extension of interval between doses, or discontinuation in vulnerable people. These solutions remain a challenge for allergy doctors diverted to intensive care units or where allergy units are temporarily closed.

Sublingual immunotherapy (SLIT) gained widespread clinical use in the last two decades, as a valuable alternative to injections. Based on similar mechanisms of action, more directed to the induction of local tolerance through stimulation of oromucosal and gastrointestinal immune system, SLIT is nowadays supported by robust evidence of efficacy [2, 3, 10]. Nonetheless, not all patients respond with the same benefit and predictive biomarkers of response are still under investigation to permit the identification of the best eligible patients. To the scope and to ensure the effectiveness, the use of purified standardized high-quality extracts, unfortunately not available for all allergens, and a proper diagnostic workup are essential. SLIT is advantaged by the possibility of being self-administered, although recent high-dose native allergen tablets may require the first intake in medical office for the management of initial local symptoms and

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reassurance [1]. The risk of severe reactions, including anaphylaxis, observed in some clinical trials appears remote and counterbalanced by the opportunity of preserving disease control in the current delicate scenario [11]. Moreover, SLIT is already an option in those patients who had systemic reactions after injections and it is expected that patients already tolerating SCIT 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 exist, consisting of chemically modified extracts (allergoids) with well-established use, evidence of immunological anti-inflammatory action and clinical benefit [12, 13]. In addition, for some SLIT preparations with high safety profile, the build-up phase can be skipped to facilitate patients who are asked to independently manage the therapy at home [14].

In this problematic setting, the permanent or temporary switch to SLIT of the SCIT courses may offer an option to overcome the logistic restrictions and avoid the consequences of treatment discontinuation. Previous experiences have confirmed that this approach can successfully be performed [15]. Finally, this kind of telemedicine and remote monitoring avoid the need for patients to access hospital sites with attendant risk and reduced or redirected services (figure 1).

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

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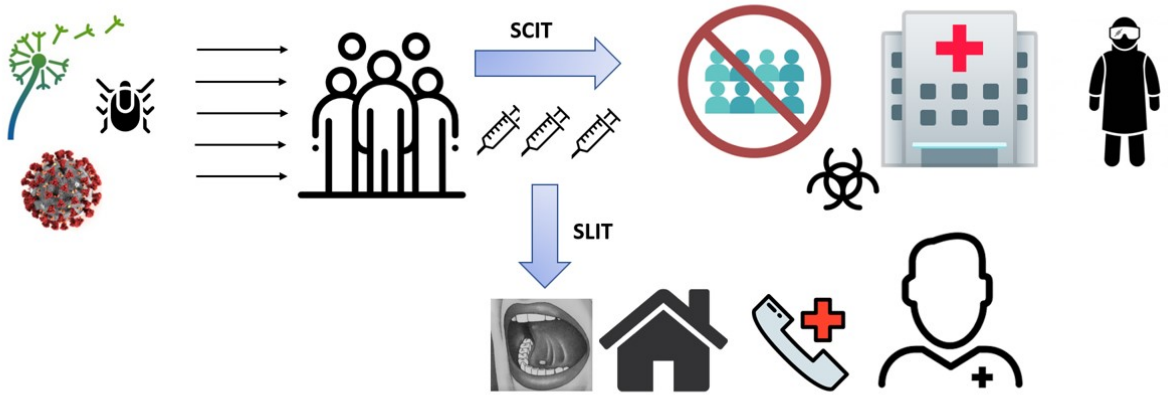
Figure. SLIT as an alternative option to SCIT for patients with restrictions on reaching their doctors or allergy units in the COVID-19 era.



Preparation -	tablets, drops, pre-dosed dispenser, monodose vial
Build-up -	NONE, 3-4 days, 4-6 days, 10 days
Maintenance -	once a week, each other day, daily
Regimen -	pre-seasonal, pre-coseasonal, continuous
Switch to SLIT-	permanent, temporary