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COVID-19 pandemic and allergen immunotherapy – an EAACI survey

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Abbreviations

- AIT, Allergen Immunotherapy
- ARIA, Allergy and Its Impact on Asthma
- COVID-19, Coronavirus disease 2019
- DGAKI, German Society of Allergy and Clinical Immunology
- EAACI, European Academy of Allergy and Clinical Immunology
- ENT, Ear-Nose-Throat
- HAART, Highly Active AntiRetroviral Therapy
- HCPs, Health Care Providers
- HIV, Human Immunodeficiency Virus
- IT IG Immunotherapy Interest Group
- SARS-CoV-2, severe acute respiratory syndrome coronavirus 2
- SCIT, Subcutaneous Immunotherapy
- SLIT, Sublingual Immunotherapy
- SmPC, Summary of Product Characteristics

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- VIT, Venom Immunotherapy
- WHO, World Health Organization

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Conflict of interest:

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Abstract

Background: As in many fields of medical care, the coronavirus disease 2019 (COVID-19) resulted in an increased uncertainty regarding the safety of allergen

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immunotherapy (AIT). Therefore, the European Academy of Allergy and Clinical Immunology (EAACI) aimed to analyze the situation in different countries and systematically collect all information available regarding tolerability and possible amendments in daily practice of sublingual AIT (SLIT), subcutaneous AIT (SCIT) for inhalant allergies and venom AIT.

Method: Under the framework of the EAACI, a panel of experts in the field of AIT coordinated by the Immunotherapy Interest Group (IT IG) set-up a web-based retrospective survey (SurveyMonkey®) including 27 standardized questions on practical and safety aspects on AIT in worldwide clinical routine.

Results: 417 respondents providing AIT to their patients in daily routine answered the survey. For patients (without any current symptoms to suspect COVID-19), 60% of the respondents informed of not having initiated SCIT (40% venom AIT, 35% SLIT) whereas for the maintenance phase of AIT, SCIT was performed by 75% of the respondents (74% venom AIT, 89% SLIT). No tolerability concern arises from this preliminary analysis. 16 physicians reported having performed AIT despite (early) symptoms of COVID-19 and/or a positive test result for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Conclusions: This first international retrospective survey in atopic diseases investigated practical aspects and tolerability of AIT during the COVID-19 pandemic and gave no concerns regarding reduced tolerability under real-life circumstances. However, the data indicate an undertreatment of AIT, which may be temporary, but could have a long-lasting negative impact on the clinical care of allergic patients.

Keywords: COVID-19, allergen immunotherapy (AIT), SARS-CoV-2, practicability, survey, safety, pandemic

Introduction

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A new strain of coronavirus (severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)) was first reported in China in December 2019 and has led to coronavirus disease 2019 (COVID-19) of global relevance (1). The disease has been diagnosed all over the globe and the World Health Organization (WHO) declared a pandemic in March, 2020 (2). To date, there are still limitations in diagnostic methods, epidemiological data and accuracy in treatments (3) (4). The wide range of clinical presentations from asymptomatic patients to multi-organic disease adds uncertainty in the prognosis and evolution (5) (6). Although the advances in the recognition of the disease and the prevention of a fatal evolution have been huge, there are still many open questions to be answered and further investigated (7). This research facilitates the best approach to this new disease and the optimal management of patients in allergy clinics and practices (8) (9) (10).

Social and economic life disruptions have been and still are very relevant. Social distancing, the use of face masks and the increase of hygiene in general and specially in hands are the cornerstone of prevention (11) (12). Moreover, our medical practices have adapted to the difficult situation, leading to a new concept in the patients' treatment (13). Practical recommendations have been developed for improvement of care of allergic patients in daily routine (14) (9) (8) (15) and telemedicine has aroused as a very valuable tool (16) (17) (18) (19) (20).

During the current pandemic, the European Academy of Allergy and Clinical Immunology (EAACI) has proposed several Position Papers and clinical recommendation for daily clinical care of allergic patients during the current pandemic e.g., (21) (22) (23), overview in (24) (25).

One of the most important therapies in allergic patients is allergen immunotherapy (AIT) as the only disease-modifying treatment option in IgE-mediated allergic diseases (26) (27). AIT has been shown to decrease symptoms, reduce the risk of developing asthma in patients with allergic rhinitis and improve quality of life and also to have long-term efficacy after cessation of the three-year course of treatment (28) (29) (30) (31). Current administration can be by subcutaneous (SCIT) injections or sublingual (SLIT) drops or tablets (32) (33). The underlying mechanisms of tolerance induction have been investigated and better understood throughout recent

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years (34). However, the ongoing COVID-19 pandemic has raised some uncertainties regarding the safety of AIT treatment under the current circumstances. One early statement of the EAACI and the "*Allergy and Its Impact on Asthma*"(ARIA-)initiative outlined practical recommendations on AIT (23). If COVID-19 is suspected or confirmed, all kinds of AIT should be temporally interrupted as a general rule in infectious diseases (33) (35) (36).

If the patient is free of symptoms without evidence of the disease, SLIT can be administered at home supported by telemedicine. This option can help in maintaining adherence to treatment as well as in follow up of allergic disease evolution and confirmation of absence of COVID-19. In an earlier clinical trial on SLIT in grass pollen-allergic Highly Active AntiRetroviral Therapy (HAART)-treated Human Immunodeficiency Virus (HIV)-positive patients were reported to be safe without any signal for any significant alteration of CD4-positive T-cell counts and HIV load (37). Concerning SCIT, it should also be continued regularly in COVID-19 symptom free patients without evidence of the disease, especially if AIT is indicated for the treatment of life-threatening conditions such as venom allergy (23). As visits to clinics can be postponed, the administration of SCIT in respiratory allergy can also be delayed a few weeks under some circumstances, to minimize in person visits at the allergy clinic. If AIT is paused due to active COVID-19 infection or due to visit restrictions (e.g. during lock-down scenarios), it should be re-initiated as soon as possible adjusting the doses properly depending on the Summary of Product Characteristics (SmPC) of the individual AIT product (33).

However, these recommendations have been proposed as experts' consensus to support the practitioner with sound standard in performing AIT during the current circumstances. Due to the nature of the pandemic these recommendations could not be based on clinical data from a prospective clinical trial. Therefore, the EAACI provided a survey to evaluate the impact of the current restrictions as well as the performance of AIT in the clinical routine. The intention of this retrospective survey was to analyze the situation in different countries worldwide and to systematically report all information gained regarding practical aspects and general tolerability of

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SLIT, SCIT and venom AIT during the pandemic. With this data reporting real-life on AIT in the current pandemic important guidances can be derived as justified measures for heading the pandemic in the future.

Methods

The corresponding author, together with the EAACI Immunotherapy Interest group members, elaborated 27 key-questions on practical aspects in AIT routine and specific tolerability under the COVID-19. These are divided into four general domains: i) basic information (Q1-Q11), ii) management of AIT in patients without any current symptoms to suspect a COVID-19 infection (Q12-Q21) and iii) management of AIT in patients despite (early) symptoms of COVID-19 infection and/or positive test result (Q22-Q26) and iv) consequences for AIT management in the 2nd half of 2020 in case that SARS-CoV-2 transmission persists (Q27). This questionnaire was then formally approved by the leadership of the EAACI and made available for physicians worldwide through the SurveyMonkey online platform (38) between July 7, 2020 and July 28, 2020, directly to an anonymized central database.

Results

Domain i) basic information (Q1-Q11)

In total, the survey was answered by 417 physicians and allied health professionals. 69% of the respondents were EAACI members, 22% EAACI Junior-members and 9% non-EAACI members. Most were physicians in Spain (9%), Mexico (6%), Italy (6%), Turkey (5%), and in other countries (all <5%) (Figure 1, *Supplementary material: Table S1*). They worked in university hospitals (42%), followed by private practices (25%), public hospitals (18%), private hospitals (9%) and others. Most of the respondents were clinicians completely or partially committed to both pediatric and adult allergic patients (48%), followed by clinicians completely or partially

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committed to adult patients only (27%) or to pediatric patients only (20%), allied health professionals (2%) and others (2%). 68% of the respondents were allergists, followed by pediatricians (12%), Ear-Nose-Throat (ENT) specialists (5%), pulmonologists (5%), internal medicine specialists (3%), dermatologists (2%) and others. Most respondents (64%) had experience in AIT for more than 10 years (*Supplementary material: Table S2*).

44% reported having national guidelines or Position Papers/Consensus Statements, whereas 46% reported not to have these documents available on the national level. In addition, 42% of the respondents reported following national or international guidelines or Position Papers/Consensus Statements for the management of AIT during the COVID-19 pandemic in daily practice and 38% reported following a similar strategy as recommended in these guidances before being aware of these documents. 42% of the respondents reported that face-to-face visits were replaced by phone calls for follow-up consultations, but to maintain consultations in newly referred patients. In contrast, almost one out of three respondent (30%) informed having replaced all face-to-face consultations by phone calls as a general rule (Table 1).

Domain ii) management of AIT in patients without any current symptoms to suspect a COVID-19 (Q12-Q21)

In this category almost 60% of the respondents reported not to initiate SCIT for inhalant allergies for the induction phase of AIT but to postpone the start of SCIT after the lockdown. 16% answered to "switch" the route of allergen-application from SCIT to SLIT and only 10% having initiated SCIT as planned (under ordinary, non-pandemic circumstances). In patients with SCIT for venom allergies, still 40% of the respondents decided to postpone the treatment to a time-window after the pandemic and only 25% reported to initiate SCIT as planned under ordinary circumstances. For SLIT, 48% of the respondents informed having initiated this therapy as planned under regular circumstances (Table 2).

For patients during the maintenance-phase of AIT-treatment (Figure 2, *Supplementary material: Table S3*), 41% of the respondents reported to continue SCIT for inhalant

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allergies, but to extend the intervals between injections whereas 33% reported continuing SCIT as planned under regular circumstances. Moreover, 13% decided to pause the treatment during the pandemic. Interestingly, 6% of the respondents informed about having switched the application route from SCIT to SLIT. For patients with venom-allergies, it was reported that SCIT was continued as planned under regular circumstances by 40% of the respondents whereas the treatment schedule was amended by 35%. Finally, a complete interruption of SCIT with venom was reported by 8% of the respondents. For SLIT in patients with inhalant allergies, 83% of the respondents informed to have continued treatment as planned under regular circumstances and a dose-reduction was reported by only 6%.

In patients without any current symptoms to suspect a COVID-19 infection, the onset of adverse reactions during AIT for inhalant allergies was reported by 4% of the respondents for SCIT and 6% for SLIT in the initiation phase of treatment whereas it was 2% for SCIT and 4% for SLIT in the maintenance phase (Table 3).

Domain iii) management of AIT in patients despite (early) symptoms of COVID-19 and/or positive test result for a SARS-CoV-2 infection (Q22-Q26)

16 out of 305 respondents answering this part of the questionnaire reported having treated patients despite (early) symptoms of COVID-19 and/or positive test result for a SARS-CoV-2 infection (Table 4). During the initiation phase of SCIT significant adverse events were reported by one physician, whereas the remaining informed that SCIT was well tolerated without increased rates of adverse events. For SLIT all respondents informed that no adverse events developed in this particular subgroup of patients treated. During the maintenance phase of AIT treatment, significant adverse events have been reported by one respondent for SCIT again whereas this has not been noted for SLIT-treated patients (Table 5).

Domain iv) strategies for AIT practical considerations in case that SARS-CoV-2 transmission persists (Q27)

The survey ended by indicating the respondents' opinions about next strategies regarding the future management of AIT for the second half of 2020 (Figure 3).

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Discussion

To the authors' knowledge, this is the first report of practical aspects and safety of AIT in a real-world setting under the current COVID-19 pandemic. Other surveys have been launched in order to understand the perception and the impact of the pandemic on patient care and decision-making in other medical disciplines such as e.g., urology, neurology and pneumology (39) (40) (41) (42). This is the first report of an international survey in the field of atopic diseases with a special focus on AIT.

More than 400 physicians and allied health professionals from all over the world have responded to the call of the EAACI. They provided (anonymized) data about their experiences with AIT during this pandemic. Most responses were received from Spain, Turkey, Mexico, and Italy (each country with more>5% of all respondents to this survey, Figure 1). A first interesting finding is that almost every 2nd respondent notified that there has been a lack of academical recommendations on AIT during the pandemic on the national level. However, available Position Papers with concrete clinical guidance (8) (9) (23) have been found to be helpful for daily routine in AIT by the majority. The EAACI-/ARIA-Position Paper on "*Handling of allergen immunotherapy in the COVID-19 pandemic*" (23) has been adapted to the national situation in German speaking countries Austria, Switzerland and Germany in a long version (43) and a pocket-guide (44). Besides a country-specific survey has been launched by the German Society of Allergy and Clinical Immunology (DGAKI) to investigate the particular situation in these countries regarding the impact of these guidelines on the clinical routine (45). Our analysis may help to further investigate national specification of AIT routine care and compliance with national recommendation. Interestingly almost 40% of the respondents reported that a similar strategy taking care of allergic patients during the pandemic had been followed

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before becoming aware of the international guidances (Table 1). This fact can be explained by the broad expertise of the participating physicians on AIT and their compliance in following evidence-based recommendations in AIT guidelines in general (31) (28).

Telemedicine such as phone-calls or videoconferences has been demonstrated as a convenient and sufficient opportunity to interact with patients remotely in certain situations e.g. to improve patient-adherence to treatment in general (46), but also to optimize care of allergic patients (17) especially in the current pandemic (16). As such, this form of consultation is an ideal tool to differentiate between allergic symptoms and COVID-19 symptoms, to triage potentially infected patients accordingly as well as to optimize and prioritize treatment in the current pandemic. Adherence to sublingual treatment in AIT as well as accuracy in self-application of biologics, have met an excellent tool in telemedicine for its follow-up and support (9) (22). The high number of more than 40% of respondents deciding to replace face-to-face visits by remote follow-up consultations (Table 1) indicates that this medium is indeed becoming a useful tool in routine patient-care. However, linked to this information has been the willingness to maintain in-person consultations for newly referred patients and for prescribing AIT. Of note, 10% stopped both first and follow-up visits and the same number of respondents maintained in-person consultations for all patients. This results may indicate that the potential of telemedicine has not been fully reached. Besides it is not clear if country-specific (economical) differences may be the reason for these heterogeneities. In an Italian real-life experience, telemedicine resulted being a valuable tool in pediatric allergy and immunology practice during the COVID-19 pandemic (10). Conversely, relevant historical information obtained (as well as diagnostic procedures) may be limited by replacing in-person consultations with telemedicine measures. As outlined above, the triage and prioritization of services and procedures provided to allergic patients may be ensured by telemedicine measures, but a better defined algorithm for key-questions adapted for this remote consultations is needed.

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The second domain of the questionnaires investigated AIT treatment in patients without any current symptoms to suspect a COVID-19 infection. In an Italian real-life experience regarding pediatric patients, only those with the first clinical evaluation of severe allergic reactions, uncontrolled allergic respiratory diseases and the ones receiving VIT, vaccines in general or biologic treatments (if not possible by a local center or at home) followed the regular schedule of face-to-face care (10).

Remarkably almost 60 % of the respondents indicated to postpone the initiation of SCIT to a time point after the pandemic (Table 2). On the other side, this fact was reported in only 35% in SLIT. The consensus report of North American experts recommends not to initiate AIT in allergic rhinitis unless there exist "*unusual circumstances, such as a patient with unavoidable exposure to a trigger that has* resulted in anaphylaxis or asthma" (8). The EAACI/ARIA guidance does not explicitly give recommendations about the initiation of both routes of AIT (23) and as a consequence a case-based decision may have followed in clinical routine by European allergists. Our analysis has revealed that only one tenth of the prescribing physicians initiated SCIT as it would be planned under regular circumstances, whereas in SLIT this was decided by every 2nd prescriber. One possible reason for the latter could be that physicians may trust more in the general safety of SLIT than SCIT especially in the initiation phase of treatment. This fact is also mirrored in 16% of physicians switching the application route from SCIT to SLIT (Table 2). However, a reduction of the initiation for both application forms alerts the general risk of relevant undertreatment of allergic patients not receiving AIT as the only available treatment option with disease-modifying potential (28) (47) (26). As a high number of patients will not receive this treatment, though clearly indicated, they may lose the interest in initiation of AIT after the end of the current pandemic. Besides, vaccines will be out of shelf life hereafter.

This alerting problem holds especially true for the treatment of venom allergic patients. For this group of patients with a potentially life-threatening allergy, AIT with venom -as planned under regular circumstances- is only offered by 25% of the respondents (Table 2). Moreover, 40% of the respondents decided to pause this treatment and postpone the begin to a time point after the current pandemic. The

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underlying background can only be speculated: one reason may be the need for in person consultations in the practice/clinic to receive the injections. AIT for venom allergy is the most effective treatment for patients with venom-allergies with much evidence supporting this treatment (30) and the consensus statement of North American experts strictly recommends the initiation of SCIT in venom allergic patients as an "*essential service*" (8).

However, the undertreatment revealed by this analysis undoubtedly may have increased the risk of patients during the recent summer to develop life-threatening reactions after an insect sting. Future evaluation of anaphylaxis cases e.g., in national and international anaphylaxis-registries may reveal this deficit of optimal, guideline-conform care of patients with this life-threatening disease (48). Krishna et al (49) reported a significant reduction in VIT initiation in a study involving 99 Adult and Pediatric Allergy and Immunology centres in the UK National Health Service. Another survey among allergy departments in Germany, Austria and Switzerland revealed a 48.5% decrease in the newly prescribed VIT from March-June 2019 to March-June 2020 period (50). A real life experience in a Portuguese reference centre revealed a marked reduction in inhalants SCIT administration (initiation suspended in 100%) with only a 2.8% continued at primary care units (51). Nevertheless, 90% of patients continued with VIT administration with none being initiated. In a Turkish survey, 31% discontinued SCIT during the pandemic with 72% being administered with longer intervals (52).

The potential risk to patients due to undertreatment of non-COVID-19 diseases has also been recently demonstrated in other indications such as heart failure (53). This analysis of the Danish nationwide administrative database revealed that the number of patients hospitalized with heart failures decreased after the lockdown in 2020 and the authors concluded that this current temporary undertreatment might indeed impact the morbidity in the future. Another web-based survey found a negative impact of the current pandemic on rheumatology practice which may lead to suboptimal control of the disease in the near future (54).

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A promising result of the analysis refers to the fact that during the maintenance phase of AIT, most physicians decided to continue SCIT as planned or with slight amendments to the treatment schedules as suggested in international position papers (Figure 2) (8) (23). Also for venom allergic patients, SCIT should not be suspended especially in potentially life-threatening conditions such as insect venom allergy in international recommendations (14) (43) (8). Furthermore, German guidance clearly emphasized that postponing initiation during the summer season is not advised and should be avoided to reduce the risk of severe reaction to an accidental sting (50). In addition almost 90% of the respondents in our survey decided to continue SLIT treatment as planned with a minority of those deciding a dose reduction (Figure 2). In this regard, the prescribing physicians have followed the European recommendations not to interrupt AIT in the maintenance period of AIT in healthy patients without clinical signs of a COVID-19 (23).

During the induction phase a low number of significant adverse-events, were reported for SCIT (3%) and SLIT (6%) in healthy patients and even less in the maintenance phase of AIT (Table 3). Taken together these analyses support data from clinical trials and real-world-evidence regarding the safety of AIT in principle when treatment-strategies are compliant with international guidelines in AIT (28) (35). A systematic meta-analysis of the EAACI demonstrated a comparable safety profile for both application forms of AIT, but could not differentiate between the initial induction and maintenance phase (55). Also, to the non-interventional nature of the retrospective analysis reported here, this survey was not able to classify adverse events in international, standardized gradings. However, it can be concluded that the data set did not indicate a signal for diminished safety of AIT during the current pandemic, in patients without clinical signs of COVID-19 or positive test results of SARS-CoV-2.

The third domain of the questionnaires investigated the safety of AIT in patients despite (early) symptoms of COVID-19. In the EAACI Position Paper (23) as well as in the German adaption (43) AIT temporary discontinuation of both SCIT and SLIT is recommended in these patients. Also, in this scenario a consensus statement of the

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Italian Society of Pediatric Allergy and Immunology indicated immediate interruption of AIT (14). The same is recommended in an Asian article by Lee et al., stating that AIT should not be re-administered until complete resolution of infection or test results are negative (56). The majority of respondents in our survey followed these recommendations as common rules (Table 4). Interestingly, those respondents informing that AIT was not interrupted have indeed not flagged-up a significant increase of adverse events in this subset of patients with a potential for an increased risk (Table 5). For SLIT treated patients none of the 14 respondents reported the onset of adverse reactions at all. For SCIT treated patients only 1 responded having experienced a notable adverse event. Clinical reports of the safety of AIT under a current viral infection are scarce in general. In a comprehensive article the limited literature of AIT in HIV patients with allergic diseases has been reviewed and found a lack of sufficient evidence for or against the application of AIT in HIV patients and further investigations collaborated by allergists together with HIV-experts has been requested (57). In one trial clinical effects and safety of SLIT with grass tablets have been investigated in 13 HIV-positive and grass-pollen allergic patients with current antiretroviral therapy (HAART) (37). The clinical outcomes for allergic symptoms and quality-of-life improved significantly compared to nine control patients, whereas no alteration of HIV viral load or CD4-positive T-cells was found. Besides SLIT in these patients demonstrated to be safe and well-tolerated. In another prospective study the effect of an influenza virus infection on standard immunological parameters during one year course of SCIT in asthmatic patients was investigated (58). The authors found that the presence of influenza-like symptoms during SCIT had not affected standard biochemical and hematological parameters (e.g., eosinophil and neutrophil counts, total IgE).

Our survey closed with an outlook for the second half of 2020 with the perception of a second wave of the pandemic leading to subsequent lockdown scenario (Figure 3). 77% of the respondents completely or strongly disagreed that AIT should not be performed which underlines their positive experience on the feasibility of AIT during the first wave in the first half of the year. However, almost 50% of the respondents

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have expressed a strong or complete agreement that AIT should only be performed in very specialized centres. This opinion may be due to uncertainity about the safety of AIT in the current pandemic in general and gives a rationale for further investigations as the one presented in this EAACI survey report.

Conclusion

The current COVID-19 pandemic significantly affects global health systems and different medical disciplines. Allergic diseases are highly prevalent and there is a critical need for optimizing care of allergic patients during the pandemic by understanding the barriers and facilitators of allergists in the clinical routine. This is especially important in allergen immunotherapy as the only available disease-modifying treatment option in allergic patients by actively modulating the immune-system.

The current report presents the results of the first international retrospective survey in allergic diseases responded by over 400 prescribers of AIT from July 7th to July 28th, 2020. The EAACI initiative aimed to investigate practical aspects and tolerability of AIT in daily routine during the COVID-19 pandemic in different regions of the world.

As for other diseases, this survey's data indicate a high grade of undertreatment for both SCIT, venom AIT and SLIT which may result in a long lasting negative impact on allergic patients' clinical care. Besides no tolerability concern arises from this preliminary analysis indicating AIT to be safe when compliant with international evidence-based guidelines and well-established treatment-algorithms. The results should help improving future guidance regarding AIT management in a pandemic scenario.

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Tables

	Responses (n=346)	%
Q9. Are there any national guidelines or Position Papers/Consensus for the management of AIT during the COVID-19 pandemic available in your country?		
Yes	153	44.22
No	160	46.24
I don't know	33	9.54
Q10. Do you follow any national or international (e.g., EAACI, WHO, AAAAI) Position Paper/Consensus for the management of AIT during the COVID-19 pandemic?		
Yes, they were helpful to decide the best strategy to follow	145	41.91
Yes, but we were already following a similar strategy	132	38.15
No, we followed a different strategy	33	9.54
I don't know	29	8.38

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Other	7	2.02
Q11. Health-care provided to your allergic patients during the COVID-19 lockdown (at the hardest moment)?		
Stop both first and follow-up consultations	33	9.54
Replace face-to-face visits by phone calls for all patients	103	29.77
Replace face-to-face visits by phone calls for follow-up, but to maintain face-to-face visits for new patients	146	42.20
Maintain face-to-face visits for all patients	36	10.40
Other	28	8.09
Q12. SCIT for inhalant allergies, please select the applied option for the initiation during the COVID-19 lockdown in general. In case of evolving conditions, select the one followed at the hardest moment of the lockdown.		

Table 1. Management of Allergen Immunotherapy practice during the COVID-19 pandemic (Q9-Q11). *AIT, Allergen Immunotherapy; COVID-19, Coronavirus disease 2019; EAACI, European Academy of Allergy and Clinical Immunology; WHO, World Health Organization; AAAAI, American Academy of Allergy, Ashtma and Immunology*

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Not to initiate, but to postpone the initiation to a time point after the pandemic	194	58.97
To initiate, but amend the up dosing schedule	23	6.99
To initiate as planned under regular circumstances	33	10.03
To initiate SLIT as alternative application route and self-administration	53	16.11
Other	26	7.90
Q13. SCIT for venom allergies (bee/wasp venom), please select the applied option for the initiation during the COVID-19 lockdown in general. In case of evolving conditions, select the one followed at the hardest moment of the lockdown.		
Not to initiate, but to postpone the initiation to a time point after the pandemic	129	39.21
To initiate, but amend the up dosing schedule	56	17.02
To initiate as planned under regular circumstances	82	24.92
Other	62	18.84
Q14. SLIT for inhalant allergies, please select the applied option for the initiation during the COVID-19 lockdown in general. In case of evolving conditions, select the one followed at the hardest moment of the lockdown.		
Not to initiate, but to postpone the initiation to a time point after the pandemic	114	34.65
To initiate, but amend the up dosing schedule, e.g. by less dosage	24	7.29
To initiate as planned under regular circumstances	158	48.02
Other	33	10.03

Table 2. Initiation of AIT in patients without symptoms to suspect COVID-19 (Q12-Q14). *AIT, Allergen Immunotherapy; COVID-19, Coronavirus disease 2019; SLIT, Sublingual Immunotherapy; SCIT, Subcutaneous Immunotherapy.*

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	Responded (n=305)	%
Q18. SCIT in the initiation period:		
SCIT was well tolerated	294	96.39
SCIT lead to significant adverse event	11	3.61
Q19. SLIT in the initiation period:		
SLIT was well tolerated	288	94.43
SLIT lead to significant adverse event	17	5.57
Q20. SCIT in the maintenance period:		
SCIT was well tolerated	299	98.03
SCIT lead to significant adverse event	6	1.97
Q21. SLIT in the maintenance period:		
Responded (n=303)	**%**	
SLIT was well tolerated	288	95.05
SLIT lead to significant adverse event	11	3.63

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Table 3. Adverse events of AIT in patients without symptoms to suspect COVID-19 (initiation and maintenance) (Q18-21) *AIT, Allergen Immunotherapy; COVID-19, Coronavirus disease 2019; SLIT, Sublingual Immunotherapy; SCIT, Subcutaneous Immunotherapy.*

Q22. Did your patients receive AIT despite (early) symptoms of COVID-19 and/or positive test result for a SARS-CoV-2 infection?		
Yes	16	5.25
No	289	94.75

Table 4. **Patients with AIT and COVID-19 symptoms and/or positive test result for SARS-CoV-2 (Q22).** *AIT, Allergen Immunotherapy; COVID-19, Coronavirus disease 2019; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2.*

	Responses (n=14)	**%**
Q23. SCIT during the initiation period:		
SCIT was well tolerated	13	92.86
SCIT lead to significant adverse event	1	7.14
Q24. SLIT during the initiation period:		

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SLIT was well tolerated	14	100
SLIT lead to significant adverse event	0	0
Q25. SCIT during the maintenance period:		
SCIT was well tolerated	13	92.86
SCIT lead to significant adverse event	1	7.14
Q26. SLIT during the maintenance period:		
SLIT was well tolerated	14	100
SLIT lead to significant adverse event	0	0

Table 5. **(Q23-Q26) Adverse events of AIT (initiation and maintenance) in patients with symptoms of COVID-19 infection and/or positive test for SARS-CoV-2.** *AIT, Allergen Immunotherapy; COVID-19, Coronavirus disease 2019; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; SLIT, Sublingual Immunotherapy; SCIT, Subcutaneous Immunotherapy.*

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Figures

Figure 1. Global distribution of respondents of survey

Figure 2. **Continuation of AIT in patients without symptoms to suspect COVID-19.** ***A, SCIT for inhalant allergies; B, SCIT for insect venom allergies; C, SLIT for inhalant allergies.*** *SCIT, Subcutaneous Immunotherapy; SLIT, Sublingual Immunotherapy.*

Figure 3. **Consequences for AIT practical considerations in second half of 2020 (if the risk for SARS-CoV-2 transmission persists)** *AIT, Allergen Immunotherapy; HCPs, Health Care Providers, SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; SCIT, Subcutaneous Immunotherapy; SLIT, Sublingual Immunotherapy.*

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Author contribution:

The corresponding author (OP), together with Montserrat Alvaro-Lozano (MAL) and the EAACI Immunotherapy Interest group members, elaborated the questionnaire which was then formally approved by the leadership of the EAACI. OP and MAL analysed

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the data and provided a first draft of this report. Hereafter, all coauthors reviewed and amended the report where applicable and gave final approval for submission.

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Figure 1_Pfaar et al.

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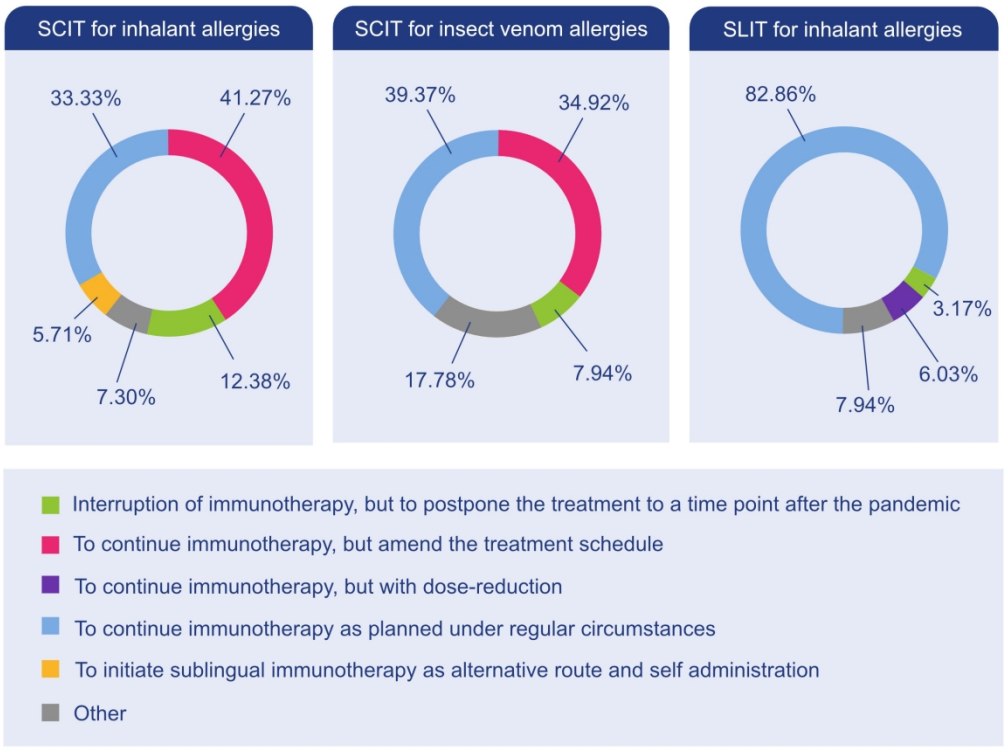


Figure 2_Pfaar et al.

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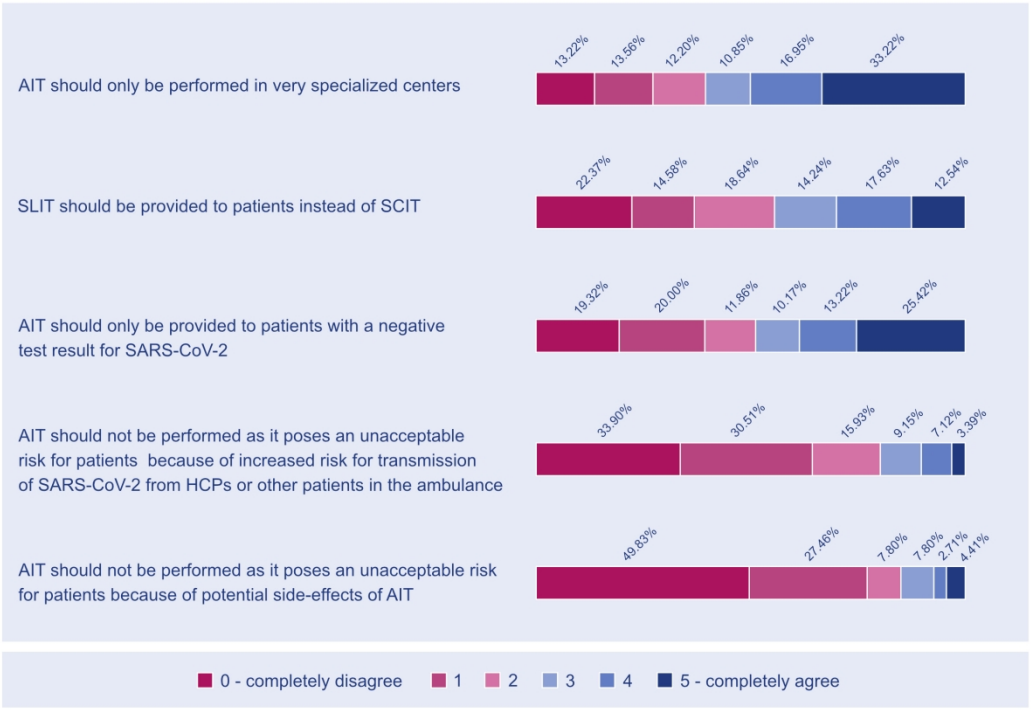


Figure 3_Pfaar et al.

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