



Aeroallergen immunotherapy associated with reduced risk of severe COVID-19 in 1095 allergic patients

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ABSTRACT

Introduction: Allergen immunotherapy (AIT) brings along changes in the immune system, restoring dendritic cell function, reducing T2 inflammation and augmenting the regulatory cell activation. Coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections, interferes with the immune system causing immune suppression during the first phase and over-activation in more advanced disease. We decided to explore the interaction of both in a real-world observational trial.

Methods: We registered COVID-19 outcomes in patients with allergic disorders in Latin America, treated with and without AIT. The registry was conducted during the first 1.3 years of the pandemic, with most of the data collected before COVID-19 vaccination was concluded in most countries. Data collection was anonymous via a web-based instrument. Ten countries participated.

Results: 630/1095 (57.6%) of the included patients received AIT. Compared to patients without AIT, those treated with AIT had a reduced risk ratio (RR) for COVID-19 lower respiratory symptoms (RR 0.78, 95% CI: 0.6703-0.9024; $p = 0.001662$) and need for oxygen therapy (RR 0.65, 95% CI: 0.4217-0.9992; $p = 0.048$). In adherent patients on maintenance sublingual immunotherapy/subcutaneous immunotherapy (SLIT/SCIT) the RR reduction was larger [RR = 0.6136 (95% CI 0.4623-0.8143; $p < 0.001$) and RR: 0.3495 (95% CI 0.1822-0.6701; $p < 0.005$), respectively]. SLIT

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was slightly more effective (NS). We excluded age, comorbidities, level of health care attendance, and type of allergic disorder as confounders, although asthma was related to a higher frequency of severe disease. When analyzing patients with allergic asthma ($n = 503$) the RR reduction favoring AIT was more pronounced with 30% for lower respiratory symptoms or worse (RR 0.6914, 95% CI 0.5264 to 0.9081, $p = 0.0087$) and 51% for need of oxygen therapy or worse (RR 0.4868, 95% CI 0.2829–0.8376, $p = 0.0082$). Among severe allergic patients treated with biologics ($n = 24$) only 2/24 needed oxygen therapy. There were no critical cases among them.

Conclusion: In our registry AIT was associated with reduced COVID-19 severity.

Keywords: COVID-19, Allergen immunotherapy, Allergic asthma, Registry, Severe COVID-19, Oxygen therapy

INTRODUCTION

With the start of the coronavirus disease (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections, early in 2020 patients with allergic disorders, treated with allergen immunotherapy (AIT), had to endure changes in the management of their treatment, as some AIT administration sites were closed or reduced in capacity for a variable duration in many countries,¹ resulting in gaps in the administration schedule.

SARS-CoV-2 impacts the immune response during the acute infection, shifting from innate immune suppression at start due to the suppression of interferon production and signaling,^{2,3} to immune over-activation, a cytokine-storm-like syndrome,⁴ and activation of the complement cascade⁵ in advanced stages of the disease³ and even in long-COVID.⁶ On the other hand, the capacity of dendritic cells to produce interferon- α is decreased in patients with allergic asthma.⁷ This and other alterations in their immune response, make allergic patients more susceptible to viral infections.⁷

Conversely, allergic patients seemed to have some protection against COVID-19, as they present a reduced concentration of the SARS-CoV-2 receptor, angiotensin-converting enzyme 2 (ACE-2), in nasal and bronchial respiratory tissues.⁸ However, more recently, the Scottish incident cohort study did show that adults with allergic asthma and a history of acute asthma 2 years prior the pandemic's start, were at increased risk

of both COVID-19 hospitalization and intensive care unit (ICU) admission or death.⁹

There have been speculations on whether AIT in allergic patients would be beneficial when facing a SARS-CoV-2 infection. Following AIT, there is an immune deviation from T-helper (Th)2 to Th1 cells – important in immunity against viruses – and Th1 cells increasingly express the antiapoptotic protein Bcl-2, prolonging their survival.¹⁰ Also, AIT in asthmatics effectively reduced the risk of lower respiratory tract infections.¹¹ Yet, solid evidence with COVID-19 is lacking. Especially in more advanced, severe COVID-19 immune over-activation is one of the prime mechanisms of damage,¹² and AIT in principle induces immune-tolerance, be it allergen-specific. However, during AIT together with the induction of T and B regulatory cells, there is also a rise in serum interleukin-10 and tumor-growth-factor- β , strong tolerogenic cytokines that could be favorable in the inflammatory phase of COVID-19.¹³

Hence, with the support of the immunotherapy and scientific committees of the *Sociedad Latinoamericana de alergia, asma e inmunología* (SLAAI) we decided to develop a registry to document the relationship between COVID-19 severity, allergic disorders, and AIT. This is an independent report of the findings.

METHODS

In cooperation with allergists, dermatologists, and otorhinolaryngologists we conducted a Latin-American registry of patients with allergic

disorders, who got infected with SARS-CoV-2. Physicians were asked to feed data into the registry as soon as they learned about COVID-19 in 1 of their patients, keeping the timespan between the actual COVID-19 infection and the retrospective data registry as short as possible. The registry used SurveyMonkey® as the data platform. We collected demographic data including information on health care level, data on the allergic conditions (rhinitis, rhinoconjunctivitis, asthma, atopic dermatitis, urticaria, among others) and data on the COVID-19 severity. Apart from that we asked the treating physician about comorbidities related to worse COVID-19 outcomes (obesity,¹⁴ diabetes,¹⁵ and hypertension¹⁶), AIT route of administration (SLIT/SCIT), phase in the AIT treatment (build-up or maintenance) and adherence to AIT.

COVID-19 was defined as confirmed if any of the intranasal tests (polymerase chain reaction–PCR, or antigen test for SARS-CoV-2) was positive and it was defined as highly suspect in patients who a). referred having had direct contact with a confirmed case AND presented anosmia or ageusia, or b). who presented anosmia or ageusia AND had at least 2 other COVID-19 related symptoms (headache, fever, excessive sweating, muscle/joint aches, cough, dyspnea).

We used a simplified COVID-19 severity scale categorizing the cases as asymptomatic; mild flu-like symptoms; moderate symptoms, no dyspnea; lower respiratory symptoms, but no need for oxygen therapy; need for oxygen therapy; critical intubated and death. "Lower respiratory symptoms" were assigned to patients treated with (increased) inhaler or nebulized therapy.

Data were collected during 13 months from October 1, 2020, until October 31, 2021 (90% of the data collection completed by the end of May 2021; at that timepoint in Latin America most subjects had not yet had an initial full vaccination scheme for COVID-19. Even so, we sub-analyzed a pre-vaccination dataset (before December 9, 2020). All data were collected anonymously. The protocol was approved by the *Comité de Ética e Investigación en Estudios en Humanos*, Médica Sur, on July 31, 2020, under the number 2020-EXT-495.

Statistical analysis

We present the results descriptively and then proceed to compare the risk of more severe forms of COVID-19 in the patients with and without AIT in the full dataset and in the early, non-vaccinated dataset. Next, we did several subgroup analyses, as age,¹⁷ type of allergic disease, or the presence of comorbidities could be confounders in the interpretation of the results; in another subgroup analysis we excluded the urticaria-only patients. We also analyzed the risk of severe COVID-19 in patients on maintenance SCIT/SLIT and the subgroup of these, reported to be adherent to AIT shortly before getting infected. For inter-group comparisons we run 2×2 contingency tables to calculate the risk ratio (RR) and its 95% confidence intervals (CI) for more severe forms of COVID-19. Pearson's chi-square tests and for small samples the two-tailed Fisher exact probability tests were applied to calculate the p-values, considering $p < 0.05$ as statistically significant.

RESULTS

A total of 1119 patients were entered into the registry. Twenty-five patients were not included due to incomplete data²¹ and 3 patients did not have any allergic disorder. Of the remaining 1095 registered patients 630 (57.5%) received AIT. Physicians indicated 79.4% of the patients were also on pharmacotherapy, be it irregular in 35%.

Characteristics of the patient population in AIT and non-AIT groups

Table 1 compares the AIT with the non-AIT group. The only differences were seen in age and allergic disorder frequency. Even so, in both groups the median age was 30–39 yrs. In the context of allergic diseases rhinitis/rhinoconjunctivitis plus asthma was more frequent in the AIT group and urticaria in the non-AIT group. Forty-three patients (3.9%) had only urticaria.

In relation to the COVID-19 diagnosis, 89.4% were confirmed and 10.6% highly suspected COVID-19 cases. Physicians reported immunoglobulin (Ig)E-mediated allergy was confirmed in 81% of the patients or clinically suspected in 16%.

	AIT (n)	AIT (%)	No AIT (n)	No AIT (%)	p
Sex	AIT (n = 630)^a	%	No AIT (n = 465)	%	
Male	310	49.2	208	44.7	NS
Female	320	50.8	257	55.3	NS
Age	AIT (n = 629)	%	No AIT (n = 465)	%	
≤9 years	86	13.7	47	10.1	NS
10-19 years	138	21.9	56	12.0	<0.0001
20-29 years	89	14.1	51	11.0	NS
30-39 years	104	16.5	113	24.3	<0.005
40-49 years	115	18.3	89	19.1	NS
50-59 years	68	10.8	64	13.8	NS
60-69 years	20	3.2	35	7.5	<0.005
70+ years	9	1.4	10	2.1	NS
Private-public health care	AIT (n = 630)	%	No AIT (n = 465)	%	
Private	452	71.7	334	71.8	NS
Public	178	28.3	131	28.2	NS
Allergic diseases	AIT (n = 630)	%	No AIT (n = 465)	%	
Rhinitis/rhino-conjunctivitis and asthma	287	45.6	139	29.9	<0.0001
Only rhino-conjunctivitis	117	18.6	76	16.3	NS
Only rhinitis	183	29	158	34.0	NS
Only asthma	34	5.4	38	8.2	NS
Atopic dermatitis	40	6.3	26	5.6	NS
Urticaria	23	3.7	62	13.3	<0.0001
Other	40	6.3	46	9.9	<0.05 ^b

Comorbidities	AIT (n = 513)	%	No AIT (n = 346)	%
Obesity	86	17.8	52	16.2
Hypertension	41	8.5	36	11.2
Diabetes melitus	28	5.8	19	5.9
None	352	72.9	232	72.3
Unknown	6	1.2	7	2.2

Table 1. Demographics in the patient group with and without allergen immunotherapy (AIT). AIT, allergen immunotherapy; NS, non significant. ^aOne patient with mild COVID and PIMS a month later was excluded from the rest of the analyses. ^bIn AIT group more rhinosinusitis. ^cIn no-AIT group more food allergy

COVID-19 severity in the AIT and non-AIT groups (including pre-vaccination analysis)

For COVID-19 severity in AIT and non-AIT groups, see Fig. 1a. When compared to allergic patients without AIT, receiving AIT was associated with a 22% risk reduction for severe COVID-19 with lower respiratory symptoms or worse (RR 0.78 [95% CI 0.6703-0.9024], $p = 0.0017$) and a risk reduction of 35% for critical COVID-19 in need of oxygen therapy or worse (RR: 0.65 [95% CI 0.42-0.9992], $p = 0.048$).

Fig. 1b presents the data for the strict pre-vaccination era (before December 2020). Receiving AIT ($n = 318$) versus not receiving AIT ($n = 269$) was associated with a risk reduction of 29% for lower airway symptoms (RR: 0.71 (95% CI 0.53-0.95; $p = 0.021$) and of 46% for oxygen therapy need or worse (RR: 0.54 (95% CI 0.29-0.99; $p = 0.04$), respectively.

There was only 1 early fatality in the non-AIT group, while 1 child in the AIT group was hospitalized more than 1 month after the mild acute illness, with the pediatric inflammatory multisystem syndrome (PIMS). This patient was not included in the further statistics of this study, as our focus is on the acute illness.

Relationship between age, AIT or non-AIT, and COVID-19 severity

As we showed in Table 1, there was a tendency for AIT patients to be more abundant in the younger age-categories. As COVID-19 severity augments with age, specifically in the sixty-plus age-group, we studied the rate of severe COVID per age-group in our population, demonstrating a tendency for lower respiratory symptoms or worse, and need for oxygen therapy or worse to be more frequent with advancing age (respectively $p < 0.005$ and $p < 0.00001$), see Table 2 and Figure E1 in the Online Repository.

Then we analyzed the relationship between the frequency of COVID-19 needing oxygen therapy or worse in the AIT and non-AIT groups subdivided into age-categories, see Fig. 2. We found a lower frequency of COVID-19 causing respiratory failure in each age-category in patients with AIT as opposed to non-AIT patients, thus demonstrating age is not a confounder in our general analysis of

	AIT Total (N)	Oxygen or worse (n)	No AIT total (N)	Oxygen or worse (n)	Risk ratio	95% confidence interval	2-tailed Fisher exact	Pearson's χ^2
1-9 years	94	4	56	3	0.794	0.185-3.420	NS	NS
10-19 years	138	2	56	1	0.826	0.076-8.931	NS	NS
20-29 years	89	0	51	4	0.000	0.000	0.016	x
30-39 years	104	11	113	7	1.707	0.688-4.240	NS	NS
40-59 years	183	15	153	27	0.465	0.257-0.841	0.012	0.009
60+ years	29	5	45	9	0.862	0.321-2.317	1.000	0.76
40+ years	212	20	198	36	0.519	0.311-0.865	0.014	0.0099

Table 2. Ratio of patients with oxygen-dependent COVID-19 with and without AIT, per age-category. AIT, allergen immunotherapy; COVID-19, coronavirus disease 2019; NS, non-significant

COVID-19 severity risk reduction associated with AIT, as in both younger and older patients there were less severe COVID-19 cases in the AIT groups versus the non-AIT groups.

Relationship between allergic disorders, with or without AIT, and COVID-19 severity

Allergic diseases were not evenly distributed among the AIT and non-AIT groups and thus could be a confounder. That is why we conducted an analysis of COVID-19 severity according to allergic disease, focusing on both diseases with a statistically significant different prevalence among AIT patients and non-AIT patients: urticaria and rhinoconjunctivitis plus asthma (ARC-asthma). There were no differences between patients with or without these allergic conditions in none of the COVID-19 severity categories, except for ARC-asthma patients more frequently suffering from COVID-19 with lower respiratory symptoms (20% versus 11%, $p < 0.0001$, see [Figure E2](#) in the Online Repository). Yet, there was no difference in the ratio needing oxygen therapy.

As urticaria without any other allergic disease has a different immune mechanism, we recalculated risk ratios for severe forms of COVID-19 in AIT and non-AIT groups deleting the 43 only urticaria patients. The risk reductions with AIT were maintained for patients on maintenance AIT, and even more so for AIT adherent patients, see [Table E2](#).

Relationship between asthma, with or without AIT, and COVID-19 severity

We also decided to analyze COVID-19 severity among patients with and without asthma (asthma alone or ARC-asthma). This time we did find a difference, with asthmatic patients being more prone to suffer more severe COVID-19, with an almost 18% elevated risk of lower respiratory symptoms ($p < 0.0001$) and a 5.3% elevated risk of oxygen therapy or worse ($p < 0.005$), see [Fig. 3a](#). As compared to patients without asthma a higher rate of asthmatic patients received AIT ($p < 0.0001$). Likewise, of all patients receiving AIT 52% has asthma, while only a 39% of the patients treated with pharmacotherapy had asthma. Analyzing all patients with asthma with and without AIT, we found no difference in

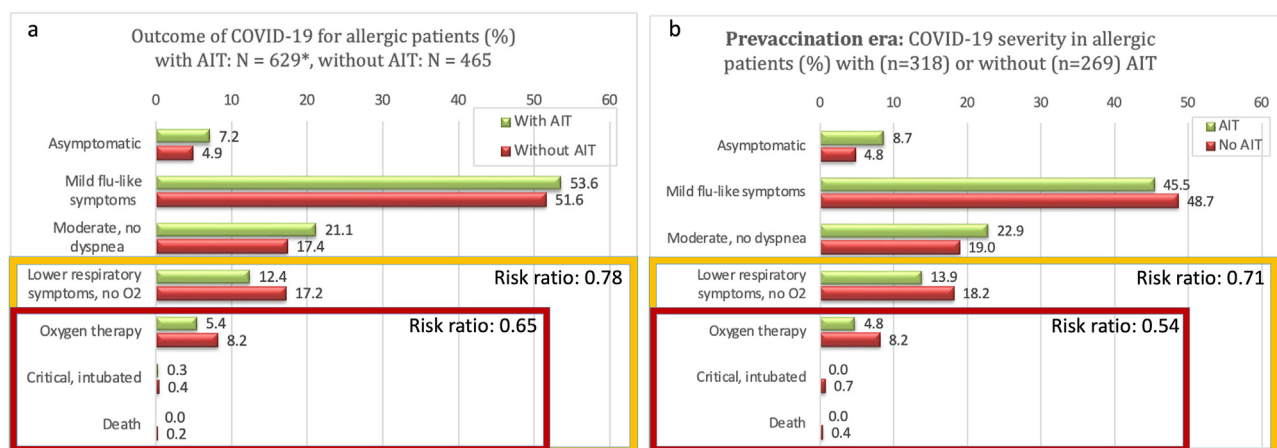


Fig. 1 a: COVID-19 severity for allergic patients with and without allergen immunotherapy. Risk of lower airway disease with AIT 22% lower (RR 0.78, 95% CI: 0.6703-0.9024; $p = 0.001662$) and for oxygen therapy or worse 35% lower (RR 0.65, 95% CI: 0.4217-0.9992; $p = 0.048$) versus no-AIT. b: same as in a, but with a cut-off for data analysis on 9th of December 2020 (pre-vaccination era). Risk of lower airway disease with AIT 29% lower (RR: 0.71 (95% CI 0.53-0.95; $p = 0.021$) and for oxygen therapy or worse 46% lower (RR: 0.54 (95% CI 0.29-0.99; $p = 0.04$) versus no-AIT. AIT, allergen immunotherapy; COVID-19, coronavirus disease of 2019; O₂, oxygen therapy. * One child was hospitalized more than a month after the acute illness, which had been mild, with severe pediatric inflammatory multisystem syndrome. This patient was not included in the statistics

asthma severity (Table E1). However, there was a marked difference in favor of the AIT group when associating it with COVID-19 severity, see Fig. 3b: in patients with asthma receiving AIT versus no-AIT we found a 30% reduction in the risk of lower airway symptoms or worse and a more than 50 percent risk reduction for needing oxygen therapy or worse.

AIT subgroups and COVID-19 severity

Association between AIT phase and adherence and COVID-19 severity

We were able to detect a dose-response relationship between the COVID-19 severity risk reduction associated with AIT. Among all AIT patients 479 were on maintenance SCIT or SLIT therapy. This subgroup of patients versus patients without AIT showed a larger risk reduction for severe COVID (with lower respiratory symptoms or worse, RR: 0.4499 (95% CI 0.2651-0.7634), $p < 0.005$) and critical COVID (needing oxygen therapy or worse, RR: 0.6659 (95% CI 0.5194-0.8538), $p < 0.005$).

Among those patients on maintenance AIT, whose physician denoted them as adherent patients in the registry, the risk reduction for severe COVID-19 was even more pronounced, see Fig. 4.

Association between AIT route of administration and COVID-19 severity

A total of 203 patients received sublingual AIT (SLIT) and 424 subcutaneous AIT (SCIT). The median age for patients receiving SLIT was 20-29 years and for SCIT 30-39 years. Comparing COVID-19 severity between SLIT and SCIT groups, we found no differences, though there seemed to be a trend for a larger reduction in the risk of lower respiratory symptoms or worse (need of oxygen

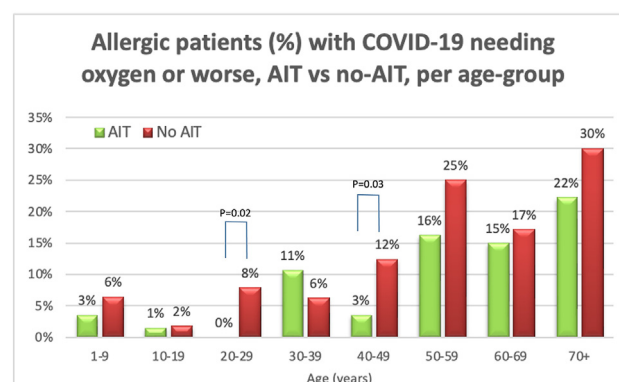


Fig. 2 Rate of allergic patients (%) with COVID-19 needing oxygen therapy or worse comparing per age-category AIT versus non-AIT groups. In all age-categories there is a lower rate of critical COVID-19 in the AIT groups. In the 20-29yo and 40-49yo categories this difference is statistically significant. (Exception 30-39yo, difference NS). AIT, allergen immunotherapy; COVID-19, coronavirus disease of 2019

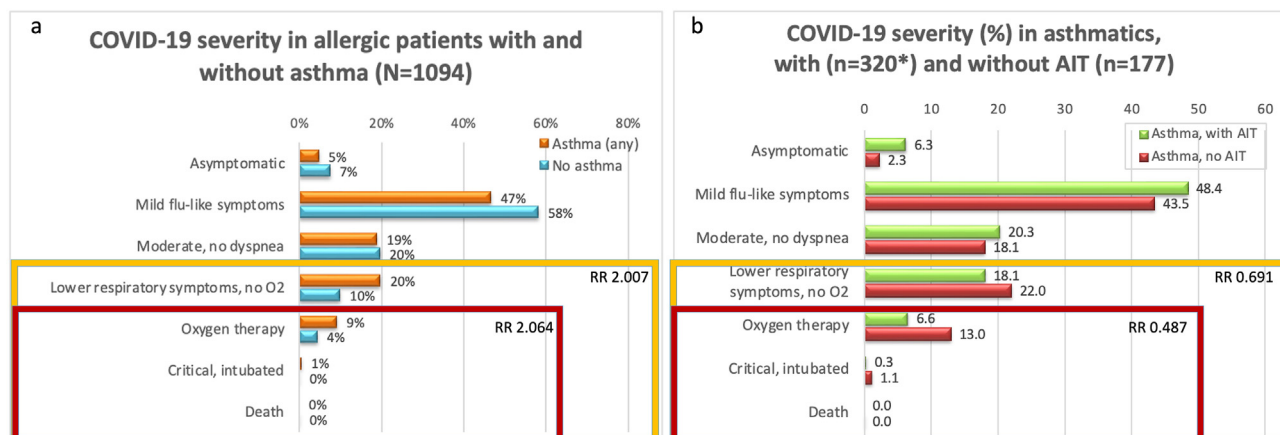


Fig. 3 a: COVID-19 severity in patients, with and without asthma. Patients with asthma ($n = 501$) were more prone to suffer from more severe COVID-19 than patients without asthma ($n = 591$). The risk of lower respiratory symptoms or worse in the asthma group was twice as high (RR 2.0067, 95% CI 1.5841–2.5422, $p < 0.0001$). Also, the risk of need for oxygen therapy or worse was twice as high in the asthma group (RR 2.0644, 95% CI 1.3179–3.2337, $p < 0.005$) as compared to allergic patients without asthma. b: Severity of COVID-19 in patients with asthma, with ($n = 320$) and without ($n = 177$) AIT. The risk of lower respiratory symptoms or worse in the AIT group was 31% less (RR 0.6914, 95% CI 0.5264 to 0.9081, $p = 0.0087$). Also, the risk of need for oxygen therapy or worse in the AIT group was 51% less (RR 0.4868, 95% CI 0.2829–0.8376, $p = 0.0082$). AIT, allergen immunotherapy; COVID-19, coronavirus disease of 2019; O2, oxygen therapy, RR, risk ratio

therapy, mechanical ventilation, or death) among the SLIT patients (Figure E3).

Biologics and COVID-19 severity

Among the registered patients there were 24 receiving biologic therapy (22 omalizumab, 1 dupilumab, 1 mepolizumab). Biologic therapy was indicated in 15/24 for asthma, 7/24 for urticaria, and 2/24 for atopic dermatitis. One-third of them

also received AIT. In relation to COVID-19 severity one-third had mild symptoms, one-third moderate symptoms, one-quarter reported lower respiratory symptoms without needing oxygen therapy and only 8% (2/24) ended up with oxygen therapy. There were no critical patients in this small, but severely allergic group. As numbers are small, we can only present results descriptively.

DISCUSSION

We present here the results of a registry of allergic patients who were infected with SARS-CoV-2 during the first year and a half of the pandemics, and we focused on COVID-19 severity of those receiving AIT as compared to those receiving only pharmacotherapy for their allergic disorder. We were able to show a reduced risk of more severe forms of COVID-19 in the AIT-treated patients in our registry, while there was no difference between AIT and non-AIT groups in the frequency of COVID-19 severity-related comorbidities (obesity, diabetes, and hypertension) nor in the proportion of private against public patients. The association of AIT with a reduced risk for severe COVID-19 was maintained in the post-hoc analysis of the pre-vaccination era patients only.

Conversely, there was a statistically significant difference between the AIT and non-AIT group in

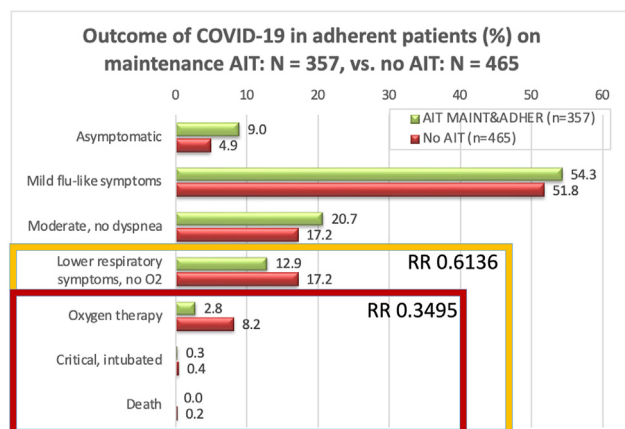


Fig. 4 Outcome of COVID-19 for allergic patients with and without allergen immunotherapy (AIT): subgroup analysis of patients on maintenance AIT, adherent to therapy versus patients with no AIT, respectively $n = 357$ and $n = 465$. Adherent patients in the maintenance AIT group had a 39% lower risk of lower airway disease (RR 0.6136, 95% CI: 0.4623–0.8143; $p = 0.0007$) and a 65% lower risk of oxygen therapy or worse (RR 0.3495, 95% CI: 0.1822–0.6701; $p = 0.0014$). ADHER, adherent to AIT therapy; AIT, allergen immunotherapy; COVID-19, coronavirus disease of 2019; MAINT, maintenance AIT therapy; O2, oxygen therapy; RR, risk ratio

relation to age, with younger age being over-represented in the AIT group. This could be a possible confounder, that might explain why AIT was related to less frequent severe and critical COVID-19. That is why we decided to analyze the frequency of more severe COVID-19 disease needing oxygen therapy or worse in the context of age. Here we clearly show that no matter to what age-category the patient belongs, there is always a lower ratio of patients with critical COVID-19 disease in the group receiving AIT. The 30-39 yo age-group is the only exception to this pattern, but the difference was non-significant. We have no explanation for this but only observe that it has been described that from this age-group, 30-year-old and onward, COVID-19 mortality shows a log-linear increase.¹⁷

Also, there was a statistically significant difference between the AIT and non-AIT groups in relation to the allergic disorder that patients were suffering from, with rhinitis or rhinoconjunctivitis plus asthma being more frequent in the AIT group. If any, there was a trend for this disorder to be linked to more frequent lower respiratory symptoms (Figure E2, first panel) and thus could not be a confounder for AIT reducing that risk in the AIT group as a whole.

On the other hand, urticaria was more frequent in the non-AIT group, as urticaria is not an indication for AIT, since the underlying mechanism is generally not via the classical IgE-mediated pathway; again, this could not be a confounder for AIT reducing the risk of more severe COVID-19, as there was no difference in COVID-19 severity in patients with or without urticaria (Figure E2, 2nd panel); nor did the overall AIT-COVID-19 severity association change when excluding patients with urticaria only (Table E2).

Then, in the context of asthma, even though there was a higher rate of patients with asthma suffering from more severe COVID-19, this subgroup was also receiving AIT at a higher rate than patients without asthma. Likewise, of all patients receiving AIT, more than half had asthma, a much higher rate than among the patients without AIT. We thus decided to do a post-hoc subgroup analysis of the asthmatic patients. The risk reduction for severe (lower airway symptoms) and critical (needing oxygen therapy) COVID-19 associated

with AIT was even stronger in patients with asthma, 31% and 51%, respectively, while these percentages were 22% and 35% for the complete dataset.

Thus, it seems to be fair to conclude AIT is associated with a reduced risk of more severe COVID-19 in general, and especially in patients with allergic asthma. Some groups have reflected on the AIT and SARS-CoV-2 interplay before taking into account that the efficacy of the innate immune response during the first phase of COVID-19 might be crucial for the final outcome.^{18,19} As already discussed in the introduction, one of the pathophysiologic mechanisms of SARS-CoV-2 at the start of an infection is repressing the initial immune response, specifically the production and effect of type I and III interferons.²⁰ Hence, the virus can replicate more easily without the interference of the host's immune system. Earlier studies had already shown that AIT helps to restore the interferon-alpha production by dendritic cells²¹ and enhance the response to infections;²² both these findings could be favorable in an allergic person when facing COVID-19.

Also, AIT augmenting the regulatory immune responses,¹⁰ adaptive and innate,^{23,24} could be beneficial in later stages of the infection to dampen the risk of developing the COVID-19 cytokine storm-like syndrome,²⁵ but these are all hypotheses that need to be tested. Definitely the area of the interplay between AIT and viral infections – and COVID-19 in particular –, both at mechanistic and epidemiologic levels is an unmet need.

We found 1 other report of COVID-19 severity in patients on AIT. There were 34/215 Turkish patients on AIT who got infected with SARS-CoV-2 since the beginning of the pandemic until the end of January 2021. The authors report no critically ill nor fatal cases among them.²⁶

In the light of the importance of not withholding AIT during the pandemics or during new rises in viral load, the American Academy of Allergy, Asthma and Immunology (AAAAI), via its COVID-19 task-force, already in May 2020 pronounced itself in favor of continuing administration of AIT.²⁷ Also, the European Academy of Allergy and Clinical Immunology (EAACI) published several papers in the early days of the pandemic and

later on with clear recommendations how to perform AIT treatment under pandemic conditions, how to retake AIT in patients that had been infected,²⁸ and practical recommendations for clinics.²⁹ Even so, a survey among EAACI members in 2021 showed a remarkably high reporting of non-initiation of AIT in candidate patients, for SCIT as high as 60%, but even for venom AIT mounting to 40%.¹ To reduce the barriers for retaking SCIT, it is important to know how to dose-adjust after a gap in its administration. This question is specifically of interest in US clinics where the vast majority uses glycerinated natural allergens for SCIT. Another AAAAI Task Force addressed this issue recently, presenting pre-pandemics practice patterns that vary considerably between rural and urban settings and academic and non-academic centers.³⁰ Past experience can guide us, but prospective studies are needed.³¹

Asthma, being a risk-factor for COVID-19 with lower airway symptoms or need for oxygen therapy or worse in our registry, is in line with findings of the recent Scottish national database, presented in the introduction.⁹ Although early reports on COVID-19 severity and asthma recognized specifically type-2 high asthma as a possible protective factor,⁸ lately there are groups of investigators showing asthma does augment COVID-19 severity risk, especially severe asthma treated with systemic corticosteroids.³² In our registry asthma severity was the same in AIT and non-AIT groups, but it did not dive into the details of asthma treatment, such as the use of systemic corticosteroids. Even with similar asthma severity in both groups (Table E1), AIT was clearly associated with a reduced frequency of severe and critical COVID-19 cases (Fig. 3b).

In this context, one could mention the lack of obtaining spirometry and data on asthma control and frequency of exacerbations as a weakness of the registry, leaving the asthma severity classification up to the investigator's judgement. Asthma severity in AIT patients could thus have been overestimated, as generally AIT is started in less severe asthma patients. Also, a weakness inherent to a registry is the selection bias of the recruited patients and another is the fact that some centers and some countries recruited a higher number of

patients, possibly reducing the generalizability of the results. Finally, the Registry was developed in the early days and did not use the later, more standardized classification for COVID-19 severity.

To reduce the risk of SARS-CoV-2 infection when attending the clinic to get one's shot, some physicians would opt for SLIT rather than for SCIT, or even propose changing from SCIT to SLIT. This seems to be a fair option, as in our registry both routes of administration showed an association with a reduced risk for COVID-19 severity. Here we could speculate that the immunological changes induced by SLIT at the site of entrance of the virus, the nasopharynx, as opposed to SCIT where those local changes are not documented,¹⁰ could possibly explain a trend seen in favor of SLIT. Nonetheless, surely many other factors must be taken into account when deciding on SLIT or SCIT.

CONCLUSION

Among the patients with allergic disorders in our registry, receiving AIT was related to a reduction in the rate of severe COVID-19, that hold stand in several subgroup analyses. The reduction in the risk of more severe COVID-19 was even stronger among allergic asthmatic patients. The decrease in risk seems to be at least as strong with SLIT as it is with SCIT. To say the least, these data appear to indicate there are no safety issue related to continuing AIT during the COVID-19 pandemic. AIT could maybe even favor the outcome of COVID-19 in allergic patients, but a controlled prospective trial should be conducted to confirm this with the most prevalent strains at this moment, ideally paying attention to the development of long-COVID and microangiopathy in patients with and without AIT.

Abbreviations

ACE-2, Angiotensin-converting enzyme 2; AIT, allergen immunotherapy; ARC, allergic rhinoconjunctivitis; CI, confidence interval; COVID-19, coronavirus disease of 2019; EAACI, European Academy of Allergy and Clinical Immunology; ICU, intensive care unit; O₂, oxygen therapy; PCR, polymerase chain reaction; RR, risk ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; SLAAI, Sociedad Latinoamericana de alergia, asma e inmunología; Th, T-helper.

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Availability of data and materials

Available at Research Gate under the following link: https://www.researchgate.net/publication/367653947_2022-1-31_COVID-19_y_alergia_All_data With <https://doi.org/10.13140/RG.2.2.16845.92641>.

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Ethics approval

The protocol was approved by the Comité de Ética e Investigación en Estudios en Humanos, Médica Sur, on July 31st, 2020, under the number 2020-EXT-495.

Authors' consent for publication

All authors gave their consent for publication of the current content of the manuscript.

Declaration of competing interest

None of the authors has any direct COI related to the content of this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.waojou.2023.100779>.

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