

## ORIGINAL ARTICLE

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# Fluctuation of Disease Severity and Quality of Life Applying Intra-lymphatic Immunotherapy for Patients with Seasonal Allergic Rhinitis

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## ABSTRACT

Allergen-specific immunotherapy is the only disease-modifying treatment for IgE-mediated allergic disorders. Intra lymphatic immunotherapy (ILIT) is an efficacious and time-saving alternative to subcutaneous immunotherapy (SCIT). This study aimed to evaluate the effects and safety of ILIT in patients with moderate to severe allergic rhinitis.

In this clinical trial, patients between 18 and 65 years old with moderate to severe allergic rhinitis were enrolled. They received monthly intra-lymphatic inguinal injections of an active allergen (1000 SQ-U *Salsola kali* pollen). Their clinical symptoms were assessed before and four weeks after treatments. The clinical signs were also evaluated during two consecutive pollination seasons and the following non-pollination season in April.

No moderate or severe reactions were recorded following ILIT treatment. Lymph node enlargement, angioedema/urticaria, and local itching were seen instantly after injection. Patients who received ILIT experienced a significant clinical improvement in self-recorded seasonal allergic symptoms after the treatments, compared to themselves before ILIT. Furthermore, their quality of life significantly improved.

This study suggests ILIT with *Salsola*-pollen extract may decrease symptoms of allergic rhinitis. It was safe and did not cause any crucial complications.

**Keywords:** Allergic rhinitis; Allergen immunotherapy; Intra-lymphatic injection

## INTRODUCTION

Allergic rhinitis is a chronic allergic disease that has become increasingly prevalent in recent decades.<sup>1</sup> Although, the exact cause of this disease is still unknown; genetic and environmental factors are

believed to play important roles.<sup>2</sup> Allergic rhinitis can significantly affect the patients' quality of life.<sup>3</sup> Regarding the Allergic Rhinitis and its Impact Asthma (ARIA) classification, allergic rhinitis is divided into intermittent and persistent with seasonal episodes often exacerbating persistent cases.<sup>4</sup>

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Non-pharmacotherapeutics treatments may reduce the allergens exposure in the patient's environment.<sup>5</sup> However, different medication classifications are usually applied in allergic rhinitis treatment.<sup>6</sup>

Recently, allergenic immunotherapy (AI) has been an effective treatment for allergic rhino conjunctivitis and allergen-induced asthma, especially in cases where patients are intolerant or unresponsive to medication.<sup>7</sup> Increasing allergen extract doses during AI can alleviate symptoms induced by allergens exposure. AI can improve the quality of life, enhance long-term tolerance to allergens, and help patients get relief from taking medicine.<sup>8,9</sup>

Before AI, it is necessary to confirm the allergic process through the skin prick test or serum level of specific IgE.<sup>10</sup> There are some methods for AI, such as subcutaneous Immunotherapy (SCIT) and sublingual Immunotherapy (SLIT).<sup>11</sup>

Intra-lymphatic immunotherapy (ILIT) is a new alternative through injecting allergens into inguinal lymph nodes three times in three months instead of conventional SCIT, in which the patient receives many injections over 3-5 years.<sup>12</sup> Compared with traditional immunotherapy, systemic reactions, and urgent problems are lower in ILIT.<sup>13</sup>

Considering the above benefits of ILIT, we evaluated this method and its side effects on our patients with allergic rhinitis who were sensitive to the *Salsola kali* allergen.

## MATERIALS AND METHODS

### Study Design

This study is a Quasi-Experimental Design to evaluate the effectiveness of ILIT in 12 patients suffering from persistent allergic rhinitis with seasonal exacerbation based on the ARIA guideline.<sup>2</sup> Our study was done over 2018- 2019 in the Allergy Clinic, Ghaem Hospital, a tertiary referral center in Mashhad in the northeast of Iran—notably, the pollination period for *Salsola kali* allergen in Iran is from September to October.<sup>14</sup>

### Patients Selection

The inclusion criteria were 18- to 65-year-old patients experiencing moderate to severe persistent allergic rhinitis with seasonal exacerbation from summer to autumn, who were symptomatic for at least two years and resistant to conventional treatment.

Besides, they should have a positive prick test for *Salsola*. *Salsola* was selected since it was the most common aeroallergen in the Middle East.<sup>14</sup> To prevent biases, we chose our cases according to their similar grade of disease severity and parallel history of medication consumption (nasal corticosteroids, oral antihistamines, nasal washing). Only patient mono-sensitized to *Salsola* were included in the study. All study procedures and potential side effects were explained to every patient, and informed written consent was obtained from those who volunteered to participate in our study. Individuals who were pregnant, suffered from any diseases other than allergic rhinitis (especially uncontrolled asthma with forced expiratory volume (FEV1) less than 70%, cardiovascular diseases, autoimmune disorders, malignancies, or a recent history of anaphylaxis), used certain medications (such as angiotensin-converting enzyme inhibitor (ACEI), monoamine oxidase inhibitor (MAOI), systemic corticosteroids, or immunosuppressing drugs), or had an upper respiratory infection were excluded from the study. We used two questionnaires to gather data Sino-nasal Outcome Test (SNOT-22) to assess clinical manifestations and Mini Rhino conjunctivitis Quality of Life Questionnaire (Mini RQLQ) to evaluate the quality of life.

### Intervention

At the first visit (April 2018), medical history, physical examination, and drug history for anti-allergic treatment were obtained from all patients; meanwhile, their questionnaires were completed. Clinical symptoms based on SNOT-22 and quality of life based on the Mini RQLQ questionnaires were assessed.

Patients were visited once a month for six months during which *Salsola* extract (Stallergenes Greer, USA) was injected monthly in inguinal lymph nodes on the second to fourth visits. The patients were admitted to the allergy-immunology ward for 24 hours and were observed for local and systemic symptoms over accurate cardiovascular monitoring. During the course of treatment, the Visual Analog Scale (VAS) is used to categorize all side effects that arise after each injection into two groups: early-onset and late-onset (occurring after one day). During the fifth visit in August, which took place four weeks after the last injection in July, all patients underwent a thorough history-taking and physical examination. Additionally, patients were assessed through questionnaires during the

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examination. Patients were evaluated in September 2018 during the pollination season. Consequently, in September 2019 and April 2020, quality of life and clinical symptoms were evaluated through the mentioned questionnaires.

To avoid any bias caused by varying pollen counts, patients were recruited in the same week for interview. The mentioned week was selected among the peaks of *Salsola* pollen season. Ultimately all these new data after the ILIT were compared with previous data before the ILIT; all the processes are summarized in Table 1.

### Statistical Analysis

For this pilot and quasi-experimental study based on the first and second types of bias (alpha: 0.05, beta: 0.2), our final case numbers were considered 15 patients. GraphPad Prism software was used to analyze the data. Kolmogorov-Smirnov test and Friedman test were used for statistical assessment. The T-test was also applied to compare VAS in different stages. The  $p \leq 0.05$  was considered significant.

## RESULTS

### Demography

The total number of patients was 15, of which seven were men, or 46.7% of the total, while the total number of women was 53.3%. The mean age was  $33.3 \pm 6.7$  years old. Side effects of intra-lymphatic injection of concentrated allergen were evaluated via VAS according to clinical observations and self-patient reports.

### Clinical Outcome Based on SNOT 22

Using the SNOT-22 questionnaire, nose, ear problems, sleep disorders, activity, and psychology were evaluated prior to ILIT and afterward, as shown in Table 2. We compared the SNOT22 total scores during the period using the pairwise test. As shown in Figure 1A, there is a significant decrease in scores after ILIT ( $p < 0.001$ ) compared to those pre-ILIT, indicating that patients' performance has improved significantly. Furthermore, a significant improvement was observed before and after immunotherapy in 2018 ( $p < 0.001$ ).

However, we found no significant difference in SNOT22 total scores after Immunotherapy and at the first pollination season ( $p = 0.08$ ). Despite the lower grades in SNOT22, there was no significant difference

between the two pollination seasons in September 2018 and September 2019. It suggests that SNOT22 scores decreased significantly between April 2018 and April 2020 after ILIT ( $p = 0.001$ ), indicating that patients experienced an overall improvement.

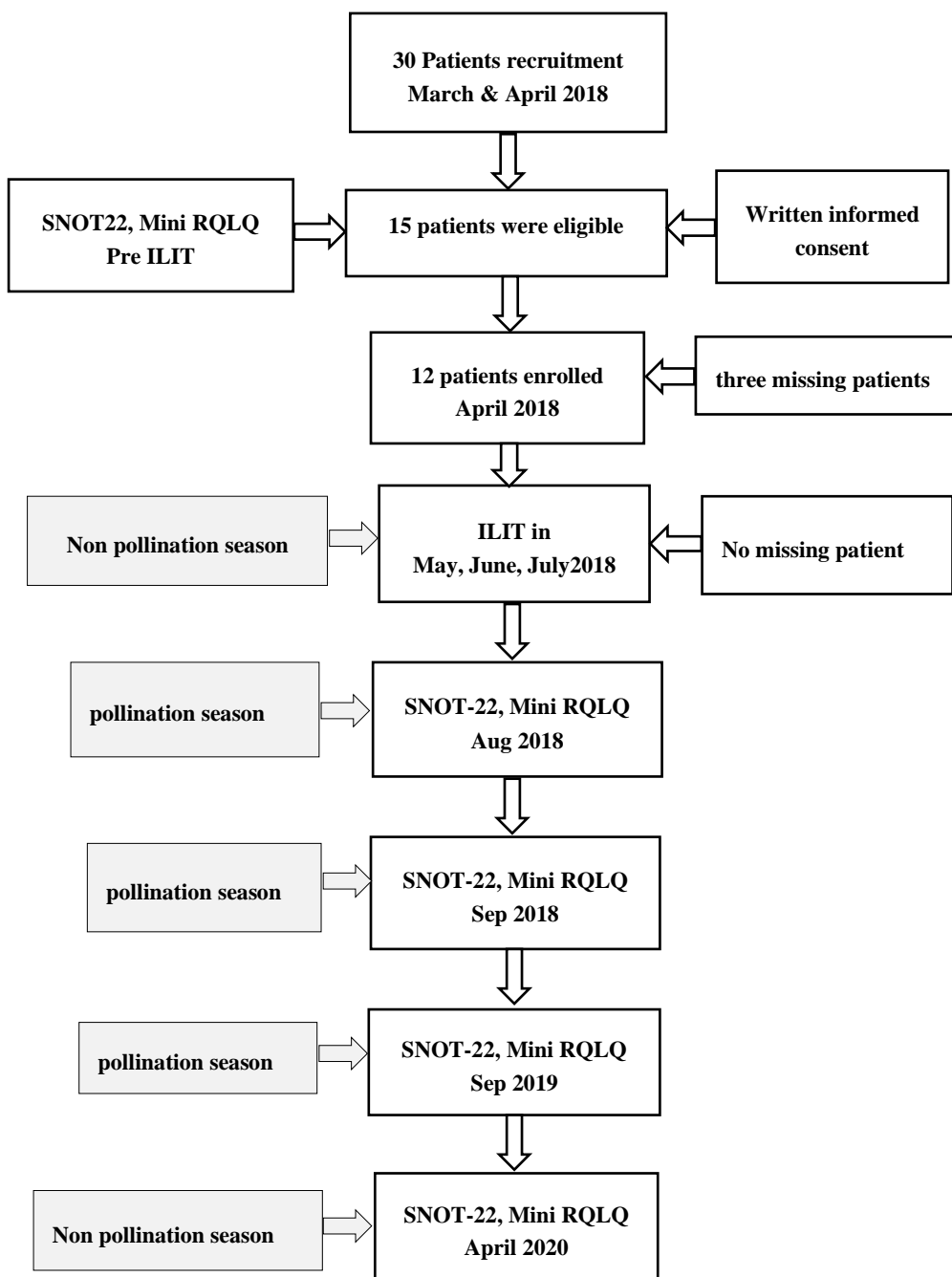
### Quality of Life Based on the Mini RQLQ Questionnaire

In the Mini RQLQ questionnaire, quality of life was measured at five points, before ILIT, four weeks after ILIT, first pollination season in the same year, next year's pollination season, and following April. Figure 2 presents the mean value for each step. There was a significant improvement in life quality between April before ILIT and August afterward, as well as September after the first pollination season ( $p < 0.001$ ). A significant improvement in their quality of life was observed comparing the first pollination season and the second one in the next year ( $p < 0.001$ ). There was also a significant difference between the before ILIT in April (2018) and after ILIT in April 2020 ( $p < 0.001$ ), and patients reported better quality of life after ILIT.

### Side Effects Based on VAS

According to VAS, side effects are calculated by percentiles based on total number of injections. Among 15 patients, lymph node enlargement was reported in 3 injections (6.7%) immediately following injection, and in 12 injections (26.7%) one day after injection. Itching at the injection site was reported 6 cases (13.3%), erythema in 6 patients (13.3%), and angioedema/urticaria in 3 injections (6.7%). The details can be seen in Table 3. The severity of pain had a mean value of  $1.5 \pm 0.5$  based on the VAS.

**Table 1. Details of the process of the investigation in the consort table**



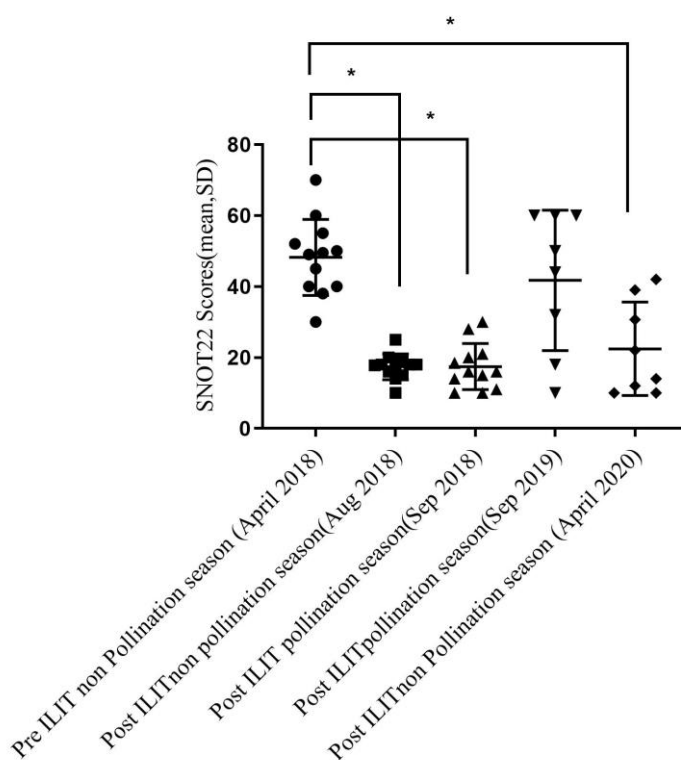
SNOT-22: Sino-nasal Outcome Test, ILIT: Intra lymphatic immunotherapy, Mini RQLQ; Quality of Life Questionnaire

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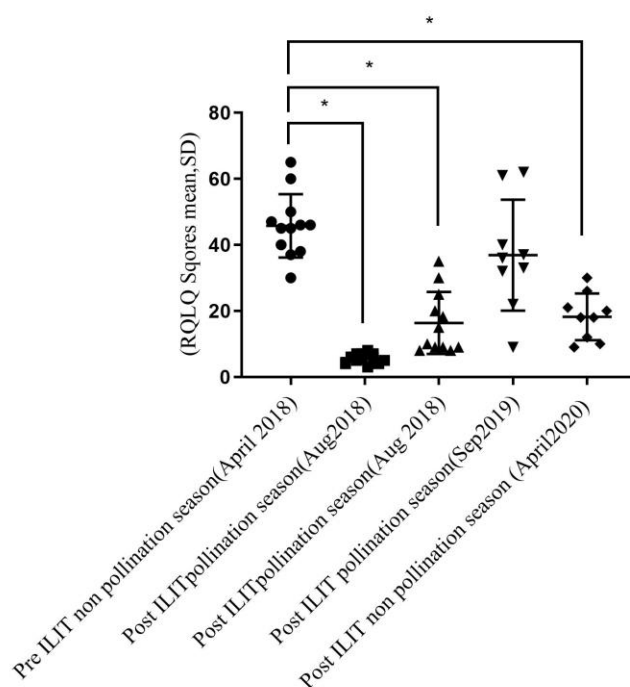
**Table 2.** Details of SNOT22 questionnaire and comparing pre ILIT and post ILIT different seasons. The significant  $p \leq 0.05$  flagged with star\*

Symptoms	Mean value Score $\pm$ SD					<i>p</i>
	Pre ILIT (April 2018)	Post ILIT (Aug 2018)	1 <sup>st</sup> Pollination (Sep 2018)	2 <sup>nd</sup> Pollination (Sep 2019)	Non-Pollination (April 2020)	
Nose	23.3 $\pm$ 6	12.1 $\pm$ 2.9	15.3 $\pm$ 6	19 $\pm$ 6.9	12.8 $\pm$ 8	0.039 *
Ear	3.3 $\pm$ 1	1 $\pm$ 0.1	1.5 $\pm$ 0.1	3 $\pm$ 3.3	1.8 $\pm$ 1	0.04*
Sleep state	9.26 $\pm$ 1.9	2.1 $\pm$ 0.2	0.8 $\pm$ 0.3	10 $\pm$ 4.2	8.4 $\pm$ 4.7	0.042*
Activity	6.13 $\pm$ 3	1.5 $\pm$ 0.1	0.5 $\pm$ 0.2	8.5 $\pm$ 7.5	4 $\pm$ 2.3	0.07
Psychology	7.51 $\pm$ 1.6	1.1 $\pm$ 0.1	0.5 $\pm$ 0.2	6.4 $\pm$ 3.8	2 $\pm$ 0.1	0.001*

SNOT-22: Sino-nasal Outcome Test, ILIT: Intra lymphatic immunotherapy



**Figure 1.** The mean score of the Sino-nasal Outcome Test (SNOT22) questionnaire pre Intra lymphatic immunotherapy (ILIT) (April, non-pollination season), post ILIT, during the first pollination season, the second one, and in the non-pollination season in April. The significant  $p \leq 0.05$  flagged with star\*



**Figure 2. Quality of life based on Mini Rhino conjunctivitis Quality of Life Questionnaire (Mini-RQLO) in pre Intra lymphatic immunotherapy (ILIT), post ILIT, at the first, the second pollination season, and in non-pollination season April. The significant  $p \leq 0.05$  flagged with star\***

**Table 3. Incidence of side effects of ILIT in our study in a total of 45 injections.**

Side effects	Early-onset N (%)	Late-onset N (%)
Lymph node enlargement	3(6.7%)	12(26.7%)
Local itching	6(13.3%)	-
Local redness	-	-
Angioedema/Urticaria	3(6.7%)	-
Nasal Symptoms	-	-
Pulmonary Symptoms	-	-
Abdominal Symptoms	-	-

ILIT: Intra lymphatic immunotherapy

### DISCUSSION

Intra-lymphatic immunotherapy is a novel approach to allergen-specific immunotherapy that involves injecting allergens directly into the lymph nodes rather than under the skin or into the muscle.<sup>12</sup> Clinical trials have shown promising results using this method, since it

allows for a lower dose of allergen to be used and can provide more rapid and sustained symptom relief.<sup>15,15</sup> Based on the SNOT-22 questionnaire, there was a significant difference between nose-ear-sinuses complications before and after immunotherapy SNOT-22 is a questionnaire that is commonly used to assess the severity of symptoms in patients with chronic

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rhinosinusitis. It includes questions about nasal congestion, facial pain, and other symptoms commonly associated with this condition.<sup>16</sup> There has been limited research available on the precise use of ILIT with SNOT-22,<sup>17</sup> and many researchers prefer to apply the Satisfaction Scale for Patients Receiving Allergen Immunotherapy Questionnaire (ESPIA).<sup>18,19</sup> Therefore, it can be one of our study weaknesses. However, ongoing clinical trials and studies are being conducted to investigate the effectiveness of ILIT for various allergies, such as allergic rhinitis and asthma. Future research may investigate the use of SNOT-22 as a tool for assessing the efficacy of ILIT in treating these conditions.<sup>20,21</sup> It was important for us to apply SNOT-22 so that we could compare the results of ILIT with our previous studies using SLIT or other types of immunotherapy.<sup>22,23</sup> It is recommended to conduct future studies simultaneously with SNOT-22 or the rhinitis assessment control test or ESPIA. According to the Mini RQLQ questionnaire, a significant difference in the quality of life was reported between before and after treatment. As well, a significant difference was observed between before immunotherapy and after the first pollination. A substantial improvement in the quality of life of enrolled patients was observed before treatment and at the end of pollination.

Some patients experienced side effects such as lymph node enlargement, local itching, and angioedema/urticaria. However, no nasal, pulmonary, or abdominal symptoms have appeared in any of the cases. Meanwhile, the patients defined a tolerable level of pain at the injection site.

ILIT was studied for the first time by Senti et al, they comprised ILIT in 58 cases versus subcutaneous immunotherapy in 54 patients using grass pollen.<sup>15</sup>

Senti et al, applied ILIT over three injections to induce cat allergy tolerance as a novel idea in 2012.<sup>24</sup> Similarly, we also used three monthly injections of ILIT to cause allergic rhinitis for *Salsola*. Our results would be compared to their findings, considering the relevant conclusions. The results of all of these studies indicated that ILIT had no moderate to severe side effects. In the present study, side effects were also mild and resolved without any treatment.

In an open pilot study, Lee et al, evaluated 11 cases of intralymphatic immunotherapy using cat and dog allergens.<sup>25</sup> Lee et al, reported two cases of anaphylaxis and one severe local reaction.<sup>26</sup> We found lymph node enlargement as an early and late side effect in a few

patients. Lymph node enlargement continued for one week and was recovered without treatment.

Hylander et al, in a double-blind study on 21 patients, performed Intra-lymphatic allergen-specific Immunotherapy for Birch pollen and grass pollen as a safe alternative treatment method for pollen-induced allergic rhinitis.<sup>25</sup> A detail of our findings considering the side effects of this method has been shown in Table 3. As seen in this table, there is no anaphylaxis, and none of our cases were excluded because of side effects.

Several years later Hylander et al, tested intralymphatic allergen-specific immunotherapy on 20 active patients versus 15 placebo cases for Birch pollen and grass pollen-induced rhinoconjunctivitis.<sup>27</sup> The pain score was defined from zero to ten based on the VAS. The mean value for pain score was  $1.15 \pm 0.5$  in our study, which is in contrast to 0.4 for Hylander's result.<sup>27</sup> Different *Salsola* allergen extracts in our study may result in different pain severity. Recently, most scientists believe ILIT can improve quality of life and resolve most allergic rhino conjunctivitis problems. This idea has been proved in these studies using grass pollen by Patterson et al, on eight patients,<sup>28</sup> and Lee. SP et al, on seven patients.<sup>26</sup> While our sample size was larger (12 patients), considering Mini RQLQ, the mean value for quality of life was improved from 46.2 before the ILIT to 18.3 at the end of ILIT and pollination. As a similar concept, Lee. SP et al, also reported improved quality of life before and after injections.<sup>26</sup> Another investigation on ILIT also applied the same questionnaire and found similar results. They enrolled 36 patients for birch and grass pollens. While their investigation was a controlled trial study, their results indicated a significant amelioration of the case group compared to the placebo group.<sup>29</sup>

Witten et al, in a double-anonymized study on 12 ILIT cases, showed a significant difference in Mini RQLQ due to ILIT by grass pollen.<sup>30</sup> Also, in the study, we found a significant difference in Mini RQLQ, indicating an improvement in quality of life. The SNOT-22 questionnaire had not been used in previous research, and we creatively used this item to evaluate patients' satisfaction in a detailed view. We found a significant difference for each item between before and after immunotherapy and between before and during the pollination season. Our study highlighted two consecutive pollination seasons. In the first assessment following pollination season, patients experienced similar symptoms to those experienced prior to ILIT.



On the other hand, compared to pre-ILIT in the first April, patients indicated alleviated symptoms in the following April. Comparing the second pollination season with the next April proved that ILIT can be more helpful in non-pollination seasons. However, ILIT was observed to have ameliorative effects on quality of life as indicated in 2020. Despite the recommendation of some immunologists to measure IgG4 and specific IgE to assess the response of ILIT,<sup>27,31</sup> we did not perform them due to some limitations. Moreover, this study was limited by the absence of a control group, which led to the design of a quasi-experimental study.

Due to our limited case number, it is suggested that more studies with a larger sample size be conducted on ILIT. On the other hand, we only focused on allergic rhinitis, while it is necessary to evaluate ILIT as a safe and effective method for some diseases such as asthma. This method does not require any premedication. Meanwhile, ILIT has fewer and rare side effects and is also a cost-effective approach. Therefore, many exciting benefits can motivate scientists to apply it and experience clinical improvement in various allergic disorders resistant to other treatments.

The present study concludes that ILIT can affect the clinical features of allergy and the quality of life of patients with allergic rhinitis. ILIT effects can be different in pollination and non-pollination seasons, but patients improve generally. ILIT is a cost-effective approach that may have a limited number of side effects. The results of this study can motivate allergists to apply it to achieve clinical improvement in allergic rhinitis patients who are resistant to other treatments.

#### STATEMENT OF ETHICS

This experiment has been approved by the ethics committee of the Mashhad University of Medical Science (IR.MUMS.fm.REC1395.574). Also, this clinical trial study was recorded in the Iran Registry of Clinical Trials (IRCT20161206031256N2). All patients signed a written informed consent agreement.

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#### CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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