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# Efficacy of Omega-3 Fatty Acids Supplementation versus Sublingual Immunotherapy in Patients with Bronchial Asthma

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Omega-3 fatty acids and sublingual immunotherapy have a considerable interest in the potential therapeutic value in asthmatic patients. The aim of the study was to compare the efficacy of omega-3 fatty acids and sublingual immunotherapy in treating patients with bronchial asthma and evaluate the value of IL17A as a marker for effective treatment. The effect on asthma control test (ACT), peak expiratory flow rate (PEFR), forced expiratory volume in the first second (FEV1) and serum interleukin 17A (IL17A) in patients with mild to moderate persistent asthma were measured. A total of 48 patients were enrolled and divided into two groups. Group A included 24 patients treated with sublingual immunotherapy for 6 months and group B, 24 patients given omega-3 fatty acids for 3 months. Serum level of IL17A was measured by Enzyme linked immunosorbent assay (ELISA). A statistically significant difference was demonstrated in each parameter between before and after treatment ( $p < 0.01$ , for each). Comparison between omega-3 fatty acids and sublingual immunotherapy as regards ACT, PEFR, and FEV1 and IL17A showed that omega-3 fatty acids treatment was better than sublingual immunotherapy in decreasing IL17A, but both were effective in decreasing PEFR, FEV1 and ACT. In conclusion, administration of omega-3 fatty acids and sublingual immunotherapy are promising in management of asthma.

In the course of the most recent decades the prevalence of allergic disease has steadily been rising and recent figures demonstrate that in the western world 10–25% of people are affected with allergic diseases ranging from food allergy, atopic dermatitis/ eczema, allergic rhinitis, hay fever to asthma [1, 2].

Allergic asthma is a chronic inflammatory disease in which Th2-derived cytokines (IL-4, IL-5 and IL-13), and IL-17, IL-22 and IL-9 have key roles in pathogenesis [3]. Despite the fact that IL-17A had been thought to assume an important role in neutrophil infiltration in tissues, IL-17A also contributes to allergic inflammation [4].

Allergen-specific immunotherapy (AIT) is currently the only known causal effective treatment of IgE-mediated allergy [5]. AIT is the only etiology-based therapy, which

has the power to modify the natural evolution of the allergic disease as demonstrated by prevention of both the onset of new allergic sensitizations and disease progression [6]. Sublingual immunotherapy is a well-established allergen-specific immunotherapy and a safe and effective strategy to reorient inappropriate immune responses in allergic patients [7].

Omega-3 is a group of polyunsaturated fatty acids, which are essential for human cells and should be supplied by the diet. Omega-3 fatty acids are commonly found in marine oils and fish oil is considered the best animal source. These fatty acids competitively inhibit the formation of prostaglandins and leukotrienes derived from arachidonic acid [8]. There is a growing evidence that omega-3 fatty acids have beneficial effects on asthma. In

addition, it is thought that atopic sensitization and allergic outcomes also can be prevented by fish intake during pregnancy, infancy, and childhood [9].

A number of studies have shown that omega-3 fatty acids may have beneficial effects in a number of asthma phenotypes by serving as effective inflammatory antagonists and/or pro-resolving agonists [10]. Observational studies have reported an announced a lesser rate of asthma in populations that expend large amounts of cold-water fish rich in omega-3 fatty acids. Dietary supplementation with omega-3 fatty acids in patients with asthma have also shown encouraging results [8].

The aim of our study is to compare the efficacy of omega-3 fatty acids and sublingual immunotherapy in patients with bronchial asthma and to evaluate the value of IL17A as markers to detect effective treatment of bronchial asthma.

## Patients and Methods

### Patient selection

After approval of the study protocol by Zagazig University Institutional Review Board (IRB) which addresses the guidelines for research with human subjects. Our study included patients recruited from the Allergy and Immunology Unit, Medical Microbiology and Immunology Department, Faculty of Medicine, Zagazig University. During the period from June 2017 to December 2017. 48 patients with proven mild to moderate asthma were participated in the study. Patients were excluded if allergic to seafood, taking anti-interleukins oral corticosteroid, refuse treatment, have associated infectious diseases, broncho-pulmonary disorders, other respiratory or systemic diseases, steroid-dependent, smokers, and patients on immunotherapy before the start of the study.

All patients provided written informed consent . Information about demographic data including age, sex, weight, height, and family history of atopy was collected. The selected patients were subjected to full detailed allergy history taking, skin prick test, PEFR, FEV1 and IL17A measurement. Patients were

divided into 2 groups (A and B). Group A patients were scheduled sublingual immunotherapy for 6 months. Immunotherapy treatment was divided into two periods; the build-up and maintenance phases [11]. Allergen immunotherapy extract was given as sublingual drops, which were kept under the tongue for a couple of minutes and then swallowed. The sublingual drops were administered in the morning on an empty stomach [12]. The patients were given 3 different dilutions; each was identified according to the guidelines from (American Academy for Allergy, Asthma and Immunology (AAAAI) by using different colors[11]. Group B patients were scheduled seven seas syrup, which contains 600 mg of fish oil and cod liver oil providing 450 mg of EPA and DHA. Patients took 7 ml daily that contain 180 mg EPA and 120 mg DHA required for every patient [8]. The patients came to Allergy and Immunology unit every two weeks for 3 consecutive months in group B. The participants continued their usual diet and previously prescribed asthma control regimen with inhaled corticosteroids during the intervention period. Patients took seven seas syrup due to better flavor and its accurate composition, so we prefer seven seas syrup of omega-3 fatty acids to be easily received from them.

At the beginning of the study and after 6 months of treatment in group A and 3 months of treatment in group B, blood samples were obtained from each patient and serum samples were isolated and stored at - 20°C for IL17A measurement. Patients were also evaluated for ACT. Patients with ACT >16 is controlled and uncontrolled if <16 points [13].

### PEFR and FEV1 measurement

PEFR and FEV1 were measured by PiKo-1 peak flow meter. It is a monitoring device that uses a patented pressure/flow sensor technology for PEFR and FEV1 measurement. Values of PEFR between 80 to 100 percent indicate that the asthma is under good control [14]. Values of FEV1 between 80% and 120% of the average value are considered normal [15].

### Serum IL17A measurement

IL17A was measured by ELISA (Thermo Fisher Scientific, Austria) according to manufacturer's directions with sensitivity equal to 0.5 pg/ml. In principle, Briefly, an anti-human IL-17A coating antibody is adsorbed onto microwells. Human IL-17A found in the sample or standard binds to antibodies adsorbed to the microwells. A biotin-conjugated anti-human IL-17A antibody is put and

binds to human IL-17A captured by the first antibody. Following incubation unbound biotin-conjugated anti-human IL-17A antibody is removed during a wash step. Streptavidin- HRP is added and binds to the biotin-conjugated anti-human IL-17A antibody. Following incubation unbound streptavidin-HRP is removed during a wash step, and substrate solution reactive with HRP is added to the wells. A colored product is formed in proportion to the quantity of human IL-17A found in the sample or standard. The reaction is finished by addition of acid and absorbance is measured at 450 nm. A standard curve is prepared from 7 human IL-17A standard dilutions and used to determine human IL-17A sample concentration.

#### Statistical Analysis

Data collected throughout history, basic clinical examination, laboratory investigations and outcome measures coded, were analyzed using Microsoft Excel software. Data were then imported into the Statistical Package for the Social Sciences (SPSS version 20.0) software for analysis. According to the type of data, qualitative represent as number and percentage, quantitative continues group represent by mean  $\pm$  SD, the following tests were used to test differences for significance; Differences between frequencies (qualitative variables) and percentages in groups were compared by Chi-square test. Paired t-test is a parametric statistical test for comparing means of two dependent samples of normally distributed data. The Mann-Whitney U test is a non-parametric statistical test for comparing two independent samples of non-normally distributed data. Student (t) test used to calculate differences

between quantitative variables in 2 groups in not normally distributed data. Wilcoxon signed rank test used to compare two related samples, matched samples, or repeated measurements on a single sample to assess whether their population mean ranks differ. The Spearman Rho correlation was used to compare between quantitative variables. Receiver operating characteristic (ROC) curve was used to detect the best cutoff value with optimum sensitivity and specificity. The accepted level of significance was  $>0.05$ .

## Results

The study included 48 bronchial asthma patients, 24 patients in group A and 24 patients in group B. A total of 9 males and 15 females aged between 8 and 56 years (median 30) were in group A and 4 males and 20 females aged between 13 to 60 years (median 30) were in group B.

There was statistically significant difference between before and 6 months after treatment in group A as regard mean ACT score ( $P= 0.00$ ), table (1) & figure (1). Also, there was statistically significant difference between before and 6 months after treatment in group A as regard PEFr and FEV1 ( $P=0.00$ ) as shown in table (1).

Table 1. Comparison between asthma control test (ACT), peak expiratory flow rate (PEFR) (%) and forced expiratory volume in the first second (FEV1) (%) before and after 6 months in group A.

| Variable  | Before treatment<br>Mean $\pm$ SD | After treatment<br>Mean $\pm$ SD | *P value |
|-----------|-----------------------------------|----------------------------------|----------|
| ACT score | 13.8 $\pm$ 1                      | 20.8 $\pm$ 1                     | 0.000    |
| PEFR      | 65.1 $\pm$ 2.2                    | 77.1 $\pm$ 1.8                   | 0.000    |
| FEV1      | 65.7 $\pm$ 2.6                    | 77.2 $\pm$ 1.7                   | 0.000    |

Values are expressed as mean  $\pm$ SD.  $P<0.05$  is significant.

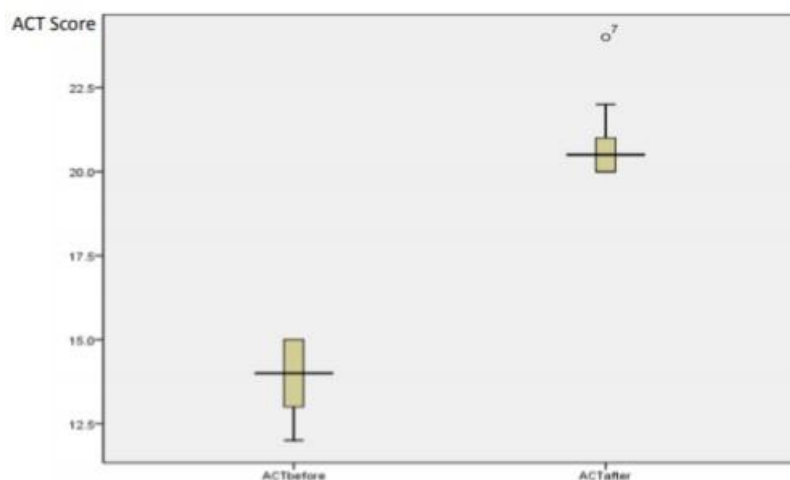


**Figure 1.** Box plot of Asthma control test score before and 6 months after treatment in group A.

There was a statistically significant difference between before and 3 months after treatment in group B as regard mean

ACT score ( $P= 0.00$ ), PEFr and FEV1 ( $P=0.00$ ) as shown in table (2).

Table 2. Comparison between mean ACT score, PEFr (%) and FEV1 (%) before and 3 months after treatment in group B.

| Variable | Before treatment<br>Mean $\pm$ SD | After treatment<br>Mean $\pm$ SD | *P value |
|----------|-----------------------------------|----------------------------------|----------|
| ACT      | 13.7 $\pm$ 1                      | 21.1 $\pm$ 1.2                   | 0.000    |
| PEFR     | 64.4 $\pm$ 1.9                    | 76.8 $\pm$ 1.8                   | 0.000    |
| FEV1     | 65.2 $\pm$ 2.7                    | 77.2 $\pm$ 1.9                   | 0.000    |

\* $P < 0.05$  is significant

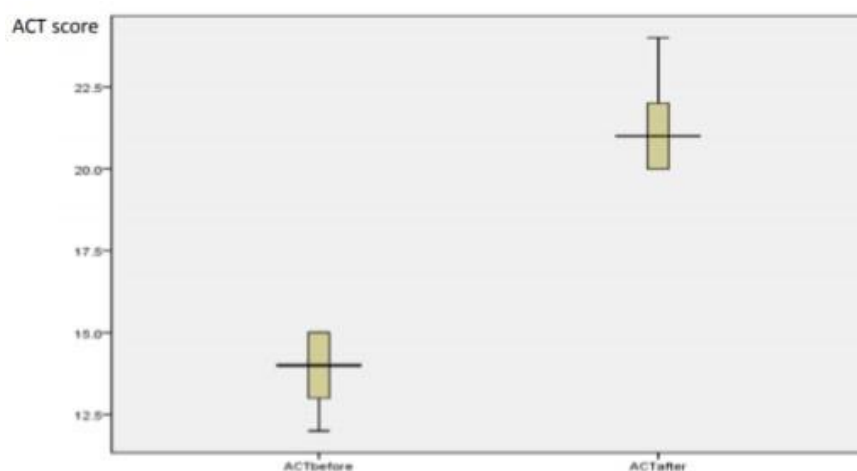


**Figure 2.** Box plot of Asthma control test score before and after treatment in group B.

Comparison between IL17A before and after 6 months in group A was summarized in table (3). As shown, there was highly

statistically significant difference between before and after 6 months in group A as regard IL17A.

Table 3. Comparison between IL17A (pg/ml) level before and 6 months after treatment in group A.

|        | Before treatment | After treatment | *P value |
|--------|------------------|-----------------|----------|
| IL17A  |                  |                 |          |
| Median | 7.1              | 0.7             | 0.000    |
| Range  | (0.06-60)        | (0-32)          |          |

$P < 0.05$  is significant

Comparison between IL17A before and after 3 months in group B was summarized in table (4). As shown, there was highly

statistically significant difference between before and after 3 months in group B as regard IL17A.

Table 4. Comparison between IL17A (pg/ml) before and 3 months after treatment in group B.

| Variable | Before treatment | After treatment | *P value |
|----------|------------------|-----------------|----------|
| IL17A    |                  |                 |          |
| Median   | 9.2              | 0.3             | 0.000    |
| Range    | (0.06-38)        | (0-32)          |          |

$P < 0.05$  is significant

Correlations between FEV1 and IL17A in group A, showed a negative correlation between IL17 and FEV1 as shown in table (5) figure (3).

A negative Correlation was obtained between FEV1 and IL17A in group B table (6) figure (4).

Table 5. Correlation between IL17A (pg/ml) and FEV1 (%) in group A.

|       | FEV1 group A |         |
|-------|--------------|---------|
|       | Rho          | P value |
| IL17A | -0.33        | 0.02*   |

$P < 0.05$  is significant

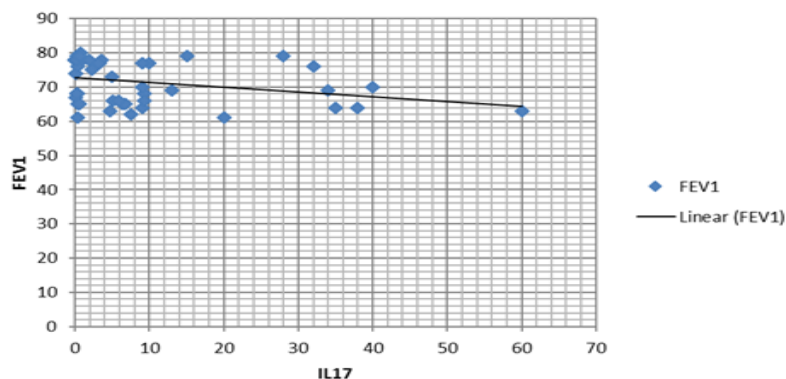


Figure 3. Correlation between IL17A (pg/ml) and FEV1(%) in group A.

Table 6. Correlation between IL17A (pg/ml) and FEV1 (%) in group B.

|       | FEV1 in group B |         |
|-------|-----------------|---------|
|       | Rho             | P value |
| IL17A | -0.47           | 0.001   |

$P < 0.05$  is significant

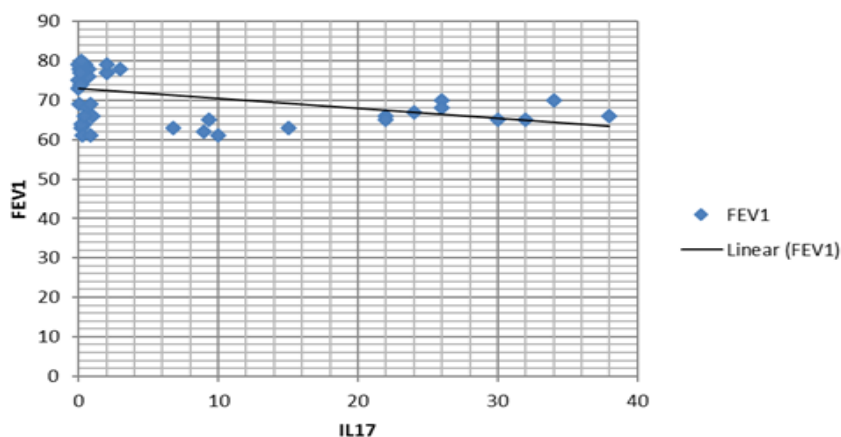


Figure 4. Correlation between IL17 (pg/ml) and FEV1(%) in group B.

The ROC curve of IL17A in group A showed that the best cut off IL17A was 2.4 pg/ml with sensitivity 91% and specificity 85% figure (5). Also, the ROC curve of

IL17A in group B showed the best cut off IL17A was 3.1 pg/ml with sensitivity 86% and specificity 77% in group B as shown in figure (6).

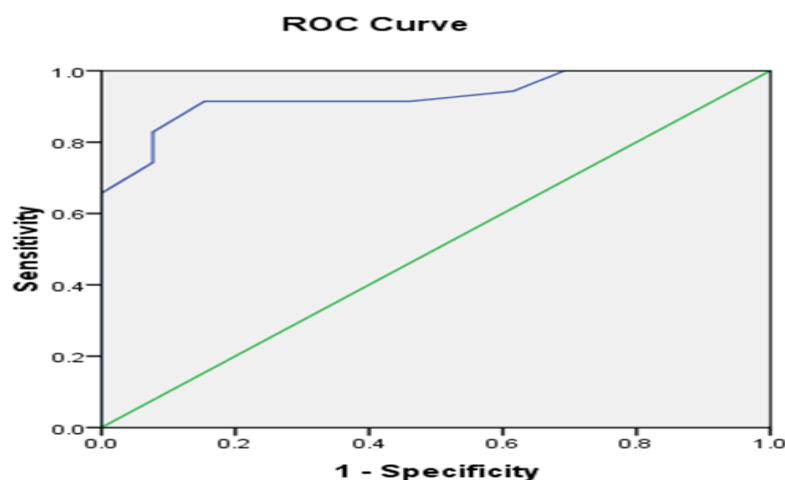


Figure 5. ROC curve of IL17A in group A.

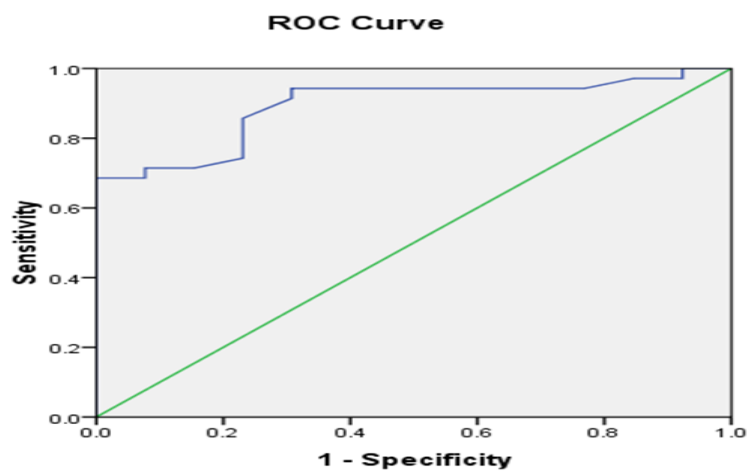


**Figure 6.** ROC curve of IL17A in group B.

Comparison between group A and group B after treatment as regard mean ACT score, PEFR and FEV1 was summarized in table (7). As shown, there was no statistically

significant difference between the two groups after treatment as regard mean ACT score, PEFR and FEV1.

Table 7. Comparison between group A and group B after treatment as regard mean ACT score, PEFR(%) and FEV1(%).

|      | Group A<br>Mean $\pm$ SD | Group B<br>Mean $\pm$ SD | P value |
|------|--------------------------|--------------------------|---------|
| ACT  | 20.7 $\pm$ 1             | 21.1 $\pm$ 1.2           | NS      |
| PEFR | 77.1 $\pm$ 1.8           | 76.8 $\pm$ 1.8           | NS      |
| FEV1 | 77.2 $\pm$ 1.8           | 77.2 $\pm$ 1.9           | NS      |

$P > 0.05$  is not significant (NS).

Comparison between group A and group B after treatment as regard IL17A was summarized in table (8). As shown, there

was statistically significant difference between the two groups after treatment as regard IL17A.

Table 8. Comparison between group A and group B after treatment as regard IL17A (pg/ml).

| Variable | Group A | Group B | *P value |
|----------|---------|---------|----------|
| IL17A    |         |         |          |
| Median   | 0.7     | 0.3     | 0.02     |
| Range    | (0-32)  | (0-32)  |          |

\* $P < 0.05$  is significant

## Discussion

Bronchial asthma is a major public health concern affecting nearly 300 million people worldwide [16]. The increasing number of people with asthma in recent decades

reflects the enormous impact of environmental factors on disease induction [17].

Allergic patients can benefit from immunotherapy as a treatment modality

which can modify the immunological response to stop reacting to involved allergens [18]. Allergen immunotherapy has the capacity to modify the natural course of disease by inducing long term immunological tolerance [19].

Air pollution and diet play documented roles in the induction and exacerbation of asthma [20, 21]. Reducing dietary antioxidants and vitamins as well as increasing the ratio of omega 6/ omega 3 polyunsaturated fatty acids in the diet are associated with asthma. Although in utero or early exposure to omega-3 fatty acids reduce childhood asthma, its effectiveness in the treatment of established asthma in humans is still controversial. Although current strategies for asthma management are highly effective, the administration of natural supplements like omega-3 is a potentially promising approach to reduce the side effects of pharmacological treatments [8].

In group A as a regard asthma control test, there was a significant improvement in asthma control test score after 6 months of treatment by sublingual immunotherapy compared to the pretreatment asthma control test score with a statistically highly significant difference. This agreed with Zhong *et al.* who performed the evaluation for sublingual immunotherapy in adult patients with allergic asthma, found that the ACT score was significantly improved [22]. Also, Tosca *et al.* found that ACT significantly improved [23].

As regards to mean levels of FEV1 in our study, there were higher mean levels of FEV1 after 6 months of treatment by sublingual immunotherapy in patients compared to pretreatment levels, with a statistically highly significant difference. This result was consistent with Ding *et al.* who found that the ratio of FEV1 and its expected value gradually increased from

before treatment to after treatment ( $P<0.01$ ) in the sublingual immunotherapy group [24]. Also, Djuric-Filipovic *et al.* found that SLIT showed a significant improvement of FEV1 ( $P = 0.036$ ), while at the same time FEV1 remain without any improvement in children on standard pharmacotherapy [25]

As regards to the mean level of PEFr in our study, there was higher mean level of PEFr after 6 months of treatment by sublingual immunotherapy compared to pretreatment levels, with a statistically highly significant difference. This result was consistent with Saporta who constituted a retrospective study that was done on asthmatic patients receiving SLIT for 6 months. The study showed a significant increase in PEFr values [26]. Also, Zhong *et al.* found that the PEFr% were significantly improved [22].

As regards to our study, levels of IL17A after 6 months of SLIT was lower than pretreatment levels with a highly statistically significant difference. This result was consistent with Ding *et al.* who found that serum IL-17 level in the case group gradually decreased from before treatment to after treatment ( $P<0.01$ ) [24].

In group B as regard to asthma control test in our study, there was a significant improvement in asthma control test score after 3 months of treatment by omega-3 fatty acids compared to the pretreatment asthma control test score with a statistically highly significant difference. This was consistent Biltagi *et al.* with who found that there was a significant improvement of ACT score in omega-3 fatty acids treatment phases when compared to the pre-treatment and placebo phases [27]. Also, this was consistent with Farjadian *et al.* who found that symptom score improved in 28 of 39 patients (72%) [8]. The daily consumption of omega-3 fatty acids had beneficial effects on clinical

symptoms of children with asthma [28]. Emelyanov *et al.* also observed Significant decrease in daytime wheezing in adult patients with atopic asthma [29].

As regards to mean levels of FEV1 in our study, there were higher mean levels of FEV1 after 3 months of treatment with omega-3 fatty acids compared to pretreatment levels, with a statistically highly significant difference. This was consistent with Biltagi *et al.* found that FEV1 showed statistically significant improvement in omega-3 fatty acids treatment phase when compared to the pretreatment and placebo phases [27]. Also, this was consistent with Farjadian *et al.* who found that there was a remarkable improvement in FEV1 [8].

As regards to the mean levels of PEFr in our study, there were higher mean levels of PEFr after 3 months of treatment by omega-3 fatty acids compared to pretreatment levels, with a statistically highly significant difference. This was consistent with Farjadian *et al.* found that there was remarkable improvement in PEFr ( $P < 0.0001$ ) [8]. Also, Emelyanov *et al.* also observed a significant increase PEFr in adult patients with atopic asthma [29].

As regards to our study, levels of IL17A after 3 months of omega-3 fatty acids were lower than pretreatment level with a highly statistically significant difference. This was consistent with Farjadian *et al.* found that IL-17A was significantly lower after treatment (both  $P = 0.049$ ) [8]. Also, Khan *et al.* found that omega-3 reduces inflammation, in part by decreasing the level of IL-17 [30].

As regards to our study, we found that there was a negative correlation between FEV1 and IL17A in both two groups. This was consistent with Farjadian *et al.* who found that there was a negative correlation between FEV1 and IL17A [8].

By ROC curve, we demonstrated that the best cut off IL17A was 2.4 with sensitivity 91% and specificity 85% in group A as well as the best cut off IL17A was 3.1 with sensitivity 86% and specificity 77% in group B. This was consistent with Bazzari *et al.* who found that the best cutoff value of IL-17A was  $> 5.39$  with sensitivity 74% and specificity 80% [31]. This is indicating that IL-17A has a primary role in pathogenesis of bronchial asthma and that IL-17A with the help of future studies can provide new lines for diagnosis and treatment of asthma.

In our study, we found that there was no significant difference between the group A and group B after treatment as regard mean ACT score, PEFr and FEV1 while there was a significant difference between the two groups after treatment as regard IL17A. This indicates that omega-3 fatty acids may be better than sublingual immunotherapy in decreasing IL17A. It may be due to a short course of omega-3 fatty acids and delay in response to sublingual immunotherapy for nearly six months. This was consistent with Farjadian *et al.* who found that IL-17A was significantly lower after treatment with omega-3 fatty acids,  $P=0.049$  for both [8].

In conclusion, sublingual immunotherapy is a well-established allergen-specific immunotherapy and a safe and effective strategy to reorient inappropriate immune responses in allergic asthma. Omega-3 fatty acids may have beneficial effects in a number of asthma phenotypes by serving as effective inflammatory antagonists and/or pro-resolving agonists. They are better than sublingual immunotherapy in decreasing IL17A, but both are effective in relieving PEFr, FEV1 and ACT.

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