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Effectiveness of montelukast in modulation of filaggrin mutation 2282del4 in atopic dermatitis Egyptian patients

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ABSTRACT

Montelukast is one of leukotriene (LT) receptor antagonists, which is safe and effective drug as a combined systemic and topical treatment regimen for treatment of moderate-to-severe atopic dermatitis (AD). The present study aimed to evaluate the role of montelukast treatment in modulation of filaggrin R501X and 2282derl4 mutations in Egyptian patients with atopic dermatitis. Total of (32) patients with AD and 16 healthy non-AD volunteers with no allergic disease were enrolled in this study. Patients were given montelukast sodium 4 mg daily for 2 weeks. SCORAD, total IgE levels and eosinophils counts were measured. Genotyping for FLG gene mutations R501X and 2282del4 were evaluated. Montelukast treatment showed significant improvement in AD patients through the reduction of serum IgE levels, blood eosinophils counts and disease severity. FLG 2282del4 mutation could be detected in 76.9% of the AD patients. FLG 2282del4 mutation was modulated in 4 out of 20 AD patients upon treatment with montelukast. Montelukast treatment could improve the skin barrier integrity through its modulatory effect on FLG mutation 2282del4 in the Egyptian patients.

INTRODUCTION

Atopic dermatitis (AD) is common chronic cutaneous disease of childhood especially in the first years of life. AD has been reported to affect more than 10% of children in many countries (Williams *et al.*, 1999). Approximately 60-70% of those with mild to severe dermatitis will continue to experience symptoms into adulthood (Lammintausta *et al.*, 1991). Patients with AD may have disrupted sleep with consequent daytime fatigue. Skin hydration, avoidance of irritants, antihistamines, topical corticosteroids and topical immune modulators are the mainstay of therapy for AD (Kagi, 2001). Most patients with AD have elevated numbers of circulating eosinophils and increased immunoglobulin E (IgE) levels and this is caused by T-cell dysfunction (Leung and Bieber, 2003). An increased frequency of T-helper2 (Th2) cells that produce increased IL-4, IL-5 and IL-13 has been demonstrated in the peripheral blood of patients with AD (Leiferman, 2001).

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Moreover, AD results from strong genetic and environmental interactions. A crucial role of the skin barrier in AD, genome-wide linkage analysis has shown a significant linkage signal with AD on chromosome 1q21 (Cookson *et al.*, 2001). This region contains the human epidermal differentiation complex (Mischke *et al.*, 1996). In humans, profilaggrin is encoded by the filaggrin (FLG) gene, which is located within the epidermal differentiation complex on chromosome 1q21 (Sandilands *et al.*, 2009).

The term "filaggrin" is derived from "filament-aggregating protein", it describes the protein's function of binding to keratin intermediate filaments causing their aggregation into macrofibrils in which the intermediate filaments are aligned in tightly packed parallel arrays and it is involved in the epidermal barrier function (Sandilands *et al.*, 2009). Its importance comes from its ability to block the entry of microbes and allergens and to control the water permeability. Loss-of-function mutations in the filaggrin gene cause the dry scaly skin condition and are strongly and significantly associated with atopic dermatitis (Van den Oord and Sheikh., 2009). Mutations in FLG (R501X and 2282del4) are reported to be strongly associated with AD and to influence asthma accompanying AD (Chen *et al.*, 2011).

Leukotrienes (LTs) are a class of potent biological inflammatory mediators. It has been shown that cysteinyl leukotrienes (cysLTs) mediate asthma and allergic rhinitis and when the LT receptors are antagonized, symptoms are resolved (De Lepeleire *et al.,* 1997). Leukotriene receptor antagonist (LTRAs) could usefully add to the available panoply of treatments available for AD (Capella *et al.,* 2001).

Literature of Rackal and Vender, (2004) provides a pathophysiological rationale for the use of cysLT receptor blockers in the treatment of AD. Montelukast is one of a LT receptor antagonist that demonstrate high-affinity binding to the cysLT1 receptor.

Montelukast is currently indicated for the prophylaxis and chronic treatment of asthma in adults and pediatric patients 12 months of age with minimal side effects (Storms *et al.,* 2011). The present study aimed to evaluate the role of montelukast treatment in modulation of filaggrin gene mutations in Egyptian patients with atopic dermatitis.

MATERIALS AND METHODS

Patients

This study was conducted in accordance with guiding principles of the Declaration of Helsinki, approved by the Ethics Committee of the Faculty of Medicine, Al-Azhar University; Consent was obtained from adult patients and the parents of pediatric patients.

A total of 48 Egyptian Kafr El-sheikh city residents, 32 patients with AD (aged 3 - 45 years; 16 male and 16 female), and 16 healthy non-AD volunteers with no allergic disease (aged 5 - 32 years; 6 male and 10 female) were enrolled in this study. AD was diagnosed according to criteria of Hanifin classification (Hanifin *et al.,* 2001). Patients were examined for evidence of AD by a physician at some dermatology clinics.

Drug used

A total 32 atopic dermatitis patients were given 1 tablet/day of (Kokast) produced by (EGYPHAR CO., Obour city, Egypt) each tablet contains montelukast sodium 4 mg for 2 weeks. During the course of the treatment there are no other treatments were given to the subjects.

Methods

Assessment of disease severity was done using the Severity Scoring of AD (SCORAD) (Kunz *et al.,* 1997).

Blood samples

Three ml of blood was collected from 32 patients (AD patients' before and four weeks after montelukast treatment) and 16 healthy volunteers. 25 µl of EDTA were added to 1 ml of blood sample and other 2 ml coagulated and centrifuged to obtain serum. Whole blood and serum was kept at -20°C. Relative differential eosinophil count; were done manually according to method described by Dacie and Lewis, (1991).

Serum IgE ELISA

Serum IgE level was measured for all participants in the study by ELISA (BioCheck, Inc., USA) according to the manufacturer's recommendations. IgE levels were calculated using standard IgE curve run on the same plate.

DNA Extraction

The genomic DNA samples were extracted from the whole blood using a commercial kit (Gene JET Whole Blood Genomic DNA Purification Mini Kit, Fermentas, Germany) according to the manufacturer’s instructions.

FLG genotyping

FLG mutation analysis was performed in 26 patients with AD (16 male and 10 female) and 8 non AD healthy control (3 male and 5 female). Genotyping for R501X and 2282del4 were performed with Platier thermal cycler (E-Enzyme, USA). Briefly, genomic DNA was amplified by means of PCR with HotStarTaq DNA Polymerase (Jena Bioscience Co., Germany). The genotyping assay was carried out by using 5 ng of genomic DNA. PCR primers were used at 167 nM final concentrations for a PCR volume of 50 µl. The PCR amplification cycles condition was carried with modification according to Weidinger and others (Weidinger *et al.,* 2006). Briefly, the R501X mutation was amplified by PCR with two primers, forward primer (5`-ACGTTGGATGCTGGAGGAAGACAAGGATCG-3`) and reverse primer (5`-ACGTTGGATGATGGTGTCCTGACCCTCTTG-3`). The PCR condition was 95 °C for 15 minutes for hot start, followed by denaturing at 95°C for 30 seconds, annealing at 56°C for 30 seconds, extension at 72 °C for 1 minute for 45 cycles, and finally incubation at 72 °C for 10 minutes. The 2282del4 mutation was typed according to the following condition. Reactions were amplified with two primers forward primer (5`-TCCCGCCACCAGCTCC-3`) and reverse primer (5`-GTGG CTCTGCTGATGGTGA-3`) as follows: 94 °C (12 minutes) for 1 cycle; 94°C (15 seconds), 58°C (30 seconds), and 72°C (45 seconds) for 30 cycles; and 72 °C (5 minutes) for 1 cycle.

Statistical analysis

Data were expressed as the mean ± standard error and were analyzed using SPSS software version 16.0. Various assay conditions were evaluated by using student T-Test (paired sample test and independent sample test). Non Parametric Test Pearson Chi-Square test was used for gene data analysis. $P < 0.05$ was defined as significant.

RESULTS

SCORAD criteria were done in order to follow the disease severity. From all investigated patients cases were categorize in to 37.5% had mild disease, 56.2% had moderate disease, and 6.3% had severed disease. Before treatment with montelukast, SCORAD score was 24.81±1.99 while after montelukast treatment it was 1.56±0.46 (Table 1). Significant (P <

0.05) lower SCORAD score was recorded after treatment with montelukast. Before treatment with montelukast high SCORAD scores were demonstrated in male and adult patients 27.56±3.05 and 28.5±4.36, respectively and low scores were recorded in female and children patients 22.0±2.35 and 23.58±2.22, respectively. No significant differences in SCORAD values based on gender (male vs. female) or based on age (adult vs. children) were detected before montelukast treatment (Table 1). After montelukast treatment significant ($P < 0.05$) change can be observed in the same gender or the same age group compared to before montelukast treatment.

Table. 1: SCORAD in atopic dermatitis Egyptian patients before and after montelukast treatment.

SCORAD	N	Before montelukast treatment	After montel ukast treatment
Patients	32	24.81±1.99	1.56±0.46*
Male	16	27.56±3.05	1.62±0.75*
Female	16	22.0±2.35	1.00±0.50*
Adult	8	28.5±4.36	2.25±1.31*
Children	24	23.58±2.22	1.41±0.46*

Data showed as mean ± SE. * *P < 0.05* indicate significant difference compared to AD patients before treatment with montelukast using student T-Test (paired sample test). N: number of patients.

Six items of eczema intensity have been selected (erythema, oedema, excoriation, crust, lichenification and dryness) and two subjective items (pruritus and sleep loss) all shown in (Fig. 1). Montelukast treatment showed significant ($P < 0.05$) differences between five items of eczema intensity (erythema, oedema, excoriation, lichenification and dryness) and two subjective items after montelukast treatment compared to those before treatment. These data indicated the effectiveness of montelukast treatment in eczema intensity and subjective improvement.

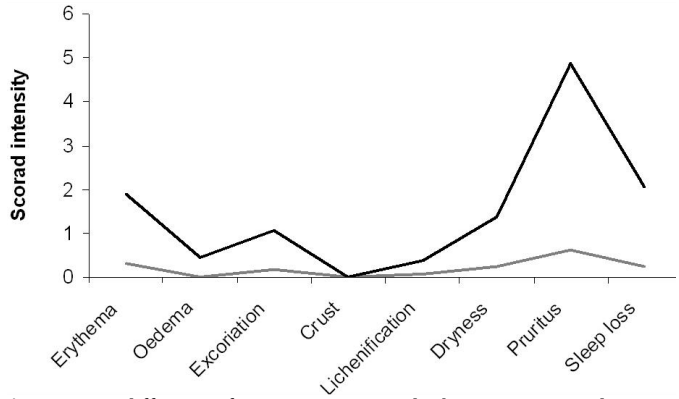

Fig. 1: Means difference of eczema intensity and subjective in atopic dermatitis Egyptian patients before and after montelukast treatment. Line in black refers to eczema intensity and subjective before montelukast treatment while line in grey refers to eczema intensity and subjective after montelukast treatment.

Furthermore, we monitored the serum level of total IgE as a biomarker of the AD (Table 2). Before montelukast treatment, the total serum IgE was 146.69±17.37 IU/mL and after treatment it was 76.62±7.38 IU/mL. Montelukast treatment significantly ($P < 0.05$) reduced the IgE levels compared to AD patients group before treatment. Non AD healthy control, total serum IgE recorded 35.12±3.44 IU/mL. Although the observed improvement in the levels of IgE upon treatment with montelukast, the IgE levels still higher when compared to the non AD controls.

Table. 2: Total IgE levels in non-atopic dermatitis control and atopic dermatitis patients before and after montelukast treatment.

Patients	N	Before montelukast treatment IgE (IU/mL)	After montelukast treatment IgE (IU/mL)	Non AD control IgE (IU/mL)
Total	32	146.69±17.37	76.62±7.38*	35.12±3.44# (n=16)
Male	16	166.25±27.99	90.62±11.59*	34.33±4.85# (n=6)
Female	16	127.12±20.0	62.62±6.63*	35.6±5.0# (n=10)
Adult	8	187.25±44.93	100.25±21.5*	40.4±3.57# (n=10)
children	24	133.17±17.27	68.75±5.86*	26.33±2.31# (n=6)

Data showed as mean±SE. * *P < 0.05* indicate significant difference compared to AD patients before treatment with montelukast using student T-Test (paired sample test). # $P < 0.05$ indicates significant difference in control non AD individuals compared to AD patients after montelukast treatment using independent t-test. N: number of patients, n: number of control non AD individuals.

Table (2) showed that before montelukast treatment, the total IgE in male was 166.25±27.99 IU/mL and in female was 127.12±20.0 IU/mL, while after montelukast treatment IgE recorded 90.62±11.59 IU/mL and 62.62±6.63 IU/mL respectively. Furthermore, before montelukast treatment, adult IgE was 187.25±44.93 IU/mL and children was 133.17±17.27 IU/mL, while after montelukast treatment IgE was 100.25±21.5 IU/mL and 68.75±5.86 IU/mL respectively. Although, IgE levels in male and adult showed higher levels than female and children, no significant difference based on gender (male vs. female) or age group (adult vs. children) was detected before or after montelukast treatment. After montelukast treatment significant ($P < 0.05$) change can be observed in the same gender or the same age group compared to before montelukast treatment. Altogether these data indicate the effectiveness of montelukast treatment in reducing the severity of the disease and control the IgE level, regardless the gender or the age group.

Eosinophils counts as another important biomarker was detected (Fig. 2). Montelukast treatment showed significant ($P < 0.05$) reduction in eosinophils count 4.2±0.83 compared to AD patients before montelukast treatment 7.6±0.67.

As FLG null alleles designed as R501X and 2282del4 were shown to be predisposing factor for AD. Twenty six patients with AD and eight non AD healthy controls were genotyped using specific primers targeting R501X and 2282del4 mutations. FLG mutation R501X was not detected either in the patients or in the control in the samples of our study. The FLG mutation 2282del4 was detected in 20 patients but not appeared in the healthy controls. The overall prevalence of FLG mutation 2282del4 in the AD patients in this study was (76.9%). Among children, the prevalence of FLG mutation 2282del4 was (88.8%). In adult

patients, the prevalence of FLG mutation 2282del4 was (15.38%). In male patients, the prevalence of FLG mutation 2282del4 was (62.5%) but, in female patients prevalence was (100%). Modulation which might be a kind of recovery in FLG mutation 2282del4 of genotyping patients was (20%) all from children (Table 3). Significant ($P < 0.05$) correlation was detected between FLG mutation 2282del4 and AD.

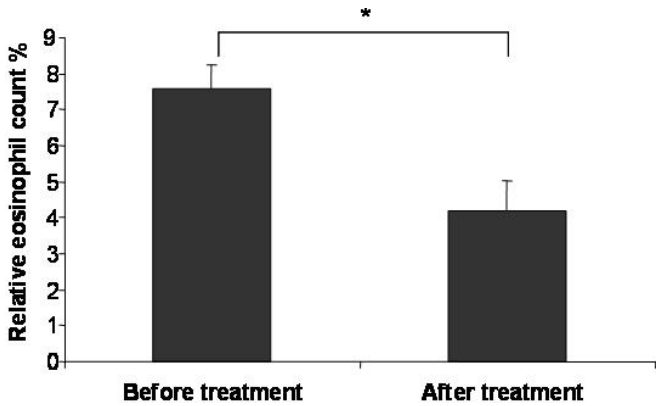

Fig 2: Effect of montelukast treatment on the relative eosinophil count before and after treatment in atopic dermatitis patients. Data showed as mean ± SE. * $P < 0.05$ indicate significant difference compared to AD patients before montelukast treatment using student T-Test (paired sample test).

Table . 3: FLG mutation 2282del4 in 26 atopic dermatitis Egyptian patients before and after montelukast treatment.

Case	Age	Sex	FLG mutation (B)	FLG mutation (A)
1	22	F	2282del4	2282del4
2	7	F	2282del4	2282del4
3	4.5	F	2282del4	WT
4	32	M	WT	WT
5	6	M	2282del4	2282del4
6	7.5	M	2282del4	2282del4
7	34	M	WT	WT
8	3.5	F	2282del4	WT
9	6	F	2282del4	2282del4
10	5	M	2282del4	2282del4
11	42	F	2282del4	2282del4
12	9	M	2282del4	WT
13	4	M	2282del4	2282del4
14	7	M	2282del4	2282del4
15	20	F	2282del4	2282del4
16	4.5	F	2282del4	2282del4
17	6.5	F	2282del4	2282del4
18	35	M	WT	WT
19	6	M	2282del4	2282del4
20	10	M	2282del4	WT
21	31	M	WT	WT
22	45	F	2282del4	2282del4
23	4	M	2282del4	2282del4
24	7	M	WT	WT
25	5.5	M	2282del4	2282del4
26	8	M	WT	WT

WT: wild type, M: male, F: female, B: before montelukast treatment, A: after montelukast treatment. The correlation between FLG mutation 2282del4 and AD was detected by Pearson Chi-Square test.

Either in AD patients with modulated FLG mutation 2282del4 or non modulated FLG, montelukast treatment showed significant ($P < 0.05$) improvement in SCORAD values and total IgE levels compared to those before montelukast treatment. A significant ($P < 0.05$) increase in total IgE levels was demonstrated before montelukast treatment in the modulated FLG mutation 2282del4 AD patients compared to none modulated FLG mutation 2282del4 AD patients, such significant increase was not detected after montelukast treatment (Table 4). Pervious results indicated that there are a kind of relation between the high efficiency of montelukast treatment to decrease the very high levels of IgE and its ability to modulate the FLG gene mutation 2282del4 in Egyptian children patients with AD.

Table. 4: Effect of montelukast treatment on SCORAD and IgE in atopic dermatitis patients with modulated and non modulated FLG mutation 2282del4.

AD patients with FLG mutation 2282del4		N	Before montelukast treatment	After montelukast treatment
SCORAD	**Modulated FLG patients**	4	33.5±2.0	0.66±0.33*
	Non modulated FLG patients	16	25.37±1.89	1.0±0.32*
IgE (IU/mL)	**Modulated FLG patients**	4	223.5±10.10#	80.5±6.0*
	Non modulated FLG patients	16	134.12±15.96	70.25±5.0*

Data showed as mean ± SE. * *P<0.05* indicate significant difference compared to AD patients before montelukast treatment using student T-Test (paired sample test). FLG: filaggrin, N: number of patients. #*P<0.05* indicate significant difference in AD patients (modulated FLG patients compared to non modulated FLG patients) using independent t-test.

DISCUSSION

Montelukast as a co-treatment with topical corticosteroids is an effective therapeutic agent for all age categories affected by moderate-to-severe AD (Broshtilova and Gantcheva, 2010). Fischer and Tsankov, (2005) demonstrated that montelukast may be helpful as a single alternative corticosteroid sparing medication in cases of severe AD, especially in patients with associated asthma and rhinitis. In this study, SCORAD values were significantly ($P < 0.05$) improved upon treatment with montelukast. Although, SCORAD tend to be higher in male vs. female and adult vs. children no significant difference based on gender or age group has been detected. Moreover, our data indicated the effectiveness of montelukast treatment in eczema intensity and relief of its subjective. The current data are consistent with the earlier investigations. For instance montelukast reduces itching, sleep disturbance, disease extent and severity (Ehlayel *et al.*, 2007). Moreover, statistical improvement in severity of AD patients using montelukast treatment compared with placebo treatment (Pei *et al.*, 2001; Eustachio *et al.*, 2002). Montelukast that cause SCORAD reductions as a monotherapy could be safe and effective drug as a combined systemic and topical treatment regimen for treatment of moderate-to-severe AD (Capella *et al.*, 2001). Improvement in: dryness, lichenification, and erythema in adult (male and female) with AD were detected upon montelukast treatment (Yanase and Kateleen, 2001). Furthermore, we demonstrated the serum level of total IgE and eosiophils counts as important biomarker of the AD. AD patient samples showed elevated eosinophils counts and high levels of the total serum IgE. Montelukast treatment significantly ($P < 0.05$), reduced the IgE

levels and relative count of eosinophils compared to AD patients group before treatment. Although, total IgE levels tend to be higher in male than female and in adult than children, no significant difference was detected based on sex or age group. Wan *et al.,* (2013) found that montelukast was associated with the decrease of IgE, LTD4 levels and severity of eosinophilic inflammation of gastrointestinal pathological lesions in mouse model. Montelukast reduced blood eosinophils count and serum IgE level in AD patient (Ehlayel *et al.,* 2007). Moreover, oral montelukast decreased the serum IgE levels and improved the clinical parameters and pulmonary function in asthmatic children (Abdel-Razik *et al.,* 2005; Stelmach *et al.,* 2005; Lee *et al.,* 2007). Leung and Bieber, (2003) reported that most patients with AD have increased IgE levels caused by T-cell dysfunction which increases IL-4 and IL-13. Montelukast treatment induced significant decrease of IL-4 and IL-13 levels which subsequently decrease the IgE levels (Ciprandi *et al.,* 2003). Furthermore, montelukast inhibited the serum total IgE as a result of the reduction in IL-4 (Gagro *et al.,* 2004). LTD4 stimulates proliferation of eosinophil hematopoietic progenitor cells, and this increase can be suppressed by montelukast as leukotriene receptor antagonists (Zhang *et al.,* 1997). Capella *et al.,* (2001) found a significant reduction in eosinophilic cationic protein (ECP) and eosinophilic protein X (EPX) levels compared to their baseline upon treatment with montelukast. Carucci *et al.,* (1998) demonstrated that montelukast induced lowering of ECP and EPX serum levels in AD patients could be related to some feedback effect of inhibition of LT synthesis on activation of eosinophils.

AD is characterized by a defective skin barrier function. Many studies have reported mutations of the skin barrier gene encoding filaggrin in a subset of patients with AD (Howell *et al.,* 2007). Study of Jeong *et al.,* (2008) has indicated that epidermal barrier dysfunction may be a key mechanism underlying elevated IgE sensitization in humans. FLG R501X mutation was not detected in our patient samples. The FLG 2282del4 mutation was demonstrated in 20 patients out of 26 genotyped patients, while it was absent in healthy non AD controls. The overall prevalence of FLG mutation 2282del4 in this study was (76.9%). In children and adult, the prevalence of FLG mutation 2282del4 was (88.8%) and (15.38%) respectively. In male and female, the prevalence of FLG mutation 2282del4 was (62.5%) and (100%) respectively. Modulation or recovery in FLG mutation 2282del4 of genotyped patients was (20%) where all are from children. The correlation between FLG mutation 2282del4 and AD showed significant ($P < 0.05$) association. In European mutations of FLG (R501X and 2282del4) were detected to be strongly associated with atopic dermatitis in an Irish population and with atopic dermatitis plus asthma in a Scottish population (Palmer *et al.,* 2006). Weidinger *et al.,* (2006) observed that associations of the FLG mutations (R501X and 2282del4) in particular with the extrinsic subtype of AD, which is characterized by high total serum IgE levels and concomitant allergic sensitizations. Furthermore, FLG mutations are significantly associated with palmar hyper-linearity in patients with AD, which represents a shared feature of AD and *ichthyosis vulgaris* (Weidinger *et al.,* 2006). The FLG mutations were present in 26.7% of patients with AD, but were also present in 14.4% of children without AD indicating that FLG mutations were weakly associated with disease severity (Morar *et al.,* 2007). Results of Morar *et al.,* (2007) provided further confirmation of the importance of mutations in FLG and the skin barrier in AD pathogenesis. Irvine *et al.,* (2011) demonstrated that stronger associations between patients who carry FLG mutations and AD (R501X 39% and 2282del4 41% in Ireland). In another study, carried out on African–American patients, 2282del4 and R501X were found with a low prevalence (3.2% each) (Winge *et al.,* 2011).

Montelukast treatment in both modulated FLG gene mutation 2282del4 AD patients and non modulated FLG gene mutation 2282del4 AD patients showed significant ($P < 0.05$) improvement in SCORAD and total IgE compared to before treatment with montelukast. In spite of the significant higher levels of IgE were recorded in AD patients with modulated FLG vs. non modulated FLG before treatment, montelukast treatment succeed in restoring the IgE levels in both groups of patients to be almost similar pattern, these data indicated that montelukast ability to modulate the FLG gene mutation 2282del4 in Egyptian children patients with AD showing higher IgE levels is more effective than those patients with lower levels of IgE. In our study, 20% of patients, all from children, with FLG mutation 2282del4 were modulated or recovered so, an interesting question arising is how montelukast modulate such FLG mutation? In general, FLG mutations were significantly higher in patients with high IgE than low IgE (Kabashima-Kubo *et al.,* 2012). Leukotriene modifiers medications prevent the effects of proinflammatory leukotrienes by either inhibition of enzymatic production of leukotrienes or by antagonism of leukotriene receptor binding (Lipworth, 1999). Wan *et al.,* (2013) reported that montelukast was associated with the decrease of IgE and LTD4 levels. Moreover, montelukast treatment induced significant decrease of IL-4 and IL-13 levels which subsequently decrease the IgE levels (Ciprandi *et al.,* 2003). Tohda *et al.,* (1999) showed in a *vitro* study that panlukast, another anti-leukotriene receptor agent, acts directly on peripheral blood mononuclear cells and can dose-dependently suppress the production of IL-4 and IL-5 in patients with bronchial asthma. Woszczek *et al.,* (2005) suggested a possible mechanism by which IL-5, IL-13, and IL-4 could modulate CysLT1 expression on eosinophils, monocytes, and macrophages, and consequently their responsiveness to LTD4, and thus contribute to the pathogenesis of asthma and allergic diseases. Acute AD skin is characterized by the over-expression of the Th2 cytokines, IL-4 and IL-13 (Howell *et al.,* 2007). Howell *et al.,* (2007) observed that filaggrin expression is increased in uninvolved AD skin as compared to acute AD skin and suggested whether these cytokines altered the expression of filaggrin. Also, previous study found that incubation of differentiated keratinocytes with IL-4 and IL-13 for 24 hours was able to down-regulate filaggrin gene expression and confirmed that IL-4 and IL-13 also down-regulates filaggrin protein expression. Howell study not only demonstrates that

filaggrin gene expression and protein are decreased in the skin of AD patients, but also indicates that this deficiency is due, in part, to the over expression of Th2 cytokines which down-regulate filaggrin expression during the differentiation process (Howell *et al.*, 2007). The atopic immune response contributes to the skin barrier defect in AD; therefore neutralization of IL-4 and IL-13 could improve skin barrier integrity (Howell *et al.*, 2007). Altogether, the ability of montelukast treatment as a leukotriene receptor antagonists and its efficiency to suppress the IL-4 and IL-13 (Th2 related cytokine) and decrease IgE levels could improve the skin barrier integrity through its modulatory effect on FLG gene mutation 2282del4 in the Egyptian patients. Further studies will be required to monitor the montelukast treatment incorporated mechanisms in the modulation of FLG gene mutation 2282del4 and FLG gene mutation 2282del4 genotype changes in the Egyptian patients with AD.

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