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Research article

The effect of treatment with fexofenadine and fluticasone propionate on the gene expression levels of Th9 transcription factors in patients with allergic rhinitis

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ABSTRACT

T helper-9 (Th9) is a new T cell subset involved in allergic rhinitis (AR) pathogenesis. Fexofenadine and fluticasone propionate are the first effective line of AR treatment. This study aimed to evaluate the effect of fexofenadine and fluticasone propionate on the gene expression levels of Interferon regulatory factor 4 (IRF4), B cell-activating transcription factor-like (BATF), and SPI1 gene-encoded protein (PU.1), essential transcription factors for Th9 cell differentiation, in AR patients. Twenty-six AR patients (aged 32.8 ± 9.1 years, 13 men and 13 women) were treated with fexofenadine and fluticasone propionate for one month. Expression levels of PU.1, IRF4, and BATF genes were measured using Real-Time PCR. Our results showed that after one month of treatment, the expression level of IRF4 and BATF genes decreased significantly ($P < 0.001$, $P < 0.01$, respectively), while PU.1 gene expression was not remarkably different. Overall, our results showed that after one month of treatment with fexofenadine and fluticasone propionate, the expression levels of IRF4 and BATF genes in AR patients decreased, which may be due to this treatment regimen. However, the exact mechanism of action of fexofenadine and fluticasone propionate needs further study.

1. Introduction

Allergic rhinitis (AR) is an Immunoglobulin E (IgE)-mediated inflammatory disease of the upper airways, characterized by sneezing, rhinorrhea, nasal congestion, and eye symptoms [1, 2]. The crucial role of helper T (Th) subsets, including Th1, Th2, Th17, and Th9 cells, as well as their cytokines and chemokines in the pathogenesis of allergic diseases such as AR, is well established [3, 4, 5, 6]. Th9 cell is a new subgroup of CD4+T cells, which can be differentiated from naive CD4+T cells in the presence of a balanced combination of transforming growth factor β (TGF-β) and interleukin-4 (IL-4) [7,8] and is characterized by strong production of IL-9 [3,9]. Th9 cells appear to be involved in the pathogenesis and severity of AR [6]. These cells have their own transcription factors for differentiation [10, 11, 12]. Although no specific transcription factor has been identified for Th9 cells, several candidate transcription factors have been proposed [13]. PU.1, a SPI1 gene-encoded protein, is a transcription factor expressed in Th9 cells in higher levels than Th1, Th2, or Th17 and involved in Th9 polarization by enhancing IL-9 expression [10]. In addition, Interferon regulatory factor 4 (IRF4) and B cell-activating transcription factor-like (BATF) are other transcription factors involved in Th9 cell differentiation and IL-9 production [14, 15]. IRF4 cooperates with BATF and binds to the *IL-9* locus, promoting Th9 cell development [12, 15].

Antihistamines and intranasal corticosteroids are the first-line therapy and the most common pharmacologic treatment options for AR [16]. Fexofenadine is a second-generation antihistamine used to reduce symptoms such as sneezing, runny nose, itchy nose, and ocular symptoms in AR patients [17, 18]. Fluticasone propionate, a topical active corticosteroid, is an effective treatment in seasonal and perennial AR patients. Fluticasone propionate significantly improves nasal symptoms, reduces the number of nasal eosinophils, basophils, and neutrophils, inhibits T cell function, and inhibits the release of cytokines from mast cells [19, 20, 21, 22, 23]. Although many studies have been conducted on investigating therapeutic benefits of intranasal corticosteroids and oral antihistamines in the treatment of AR and their mechanism of action, the effect of fexofenadine and fluticasone propionate on immune cells

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involved in the development of AR has received less attention. Considering the indispensable contribution of Th9 cells in the development of AR, to our knowledge, this is the first study that evaluated the effect of co-administration of fexofenadine and fluticasone propionate on the gene expression levels of Th9 transcription factors (PU.1, IRF4, and BATF) in the peripheral blood cells of AR patients which may help to reveal the mechanism of effectiveness of these medicines.

2. Materials and methods

2.1. Patient's characteristics

Participants in this study included 26 patients with AR (13 men and 13 women, aged 32.8 ± 9.1 years). Patients with AR were selected from those referred to Dr. Mohammad Kermanshahi Hospital from July 2019 to October 2019 by an allergist based on practical guidelines for managing allergic rhinitis [24]. None of the participants had used systemic or intranasal corticosteroids in the past three months. Participants included people with no history of other inflammatory diseases such as autoimmune diseases, infectious diseases, or cancer. In addition, pregnant women were also excluded from the study. The socio-demographic characteristics of the study participants are shown in Table 1. All participants were notified about the objectives of the study and signed informed consent. This study was conducted based on the Helsinki Declaration and was approved by the Ethics Committee of Kermanshah University of Medical Sciences (IR.KUMS.REC: 3008169). All subjects received fexofenadine (2 tablets (120mg/day) and fluticasone propionate (One puff/nostril/day (100μg/day)) for one month. Peripheral blood samples were taken from AR patients before and after treatment to assess PU.1, IRF4, and BATF expression levels.

2.2. RNA extraction, cDNA synthesis, and real-time PCR

RNA content was extracted from EDTA-containing peripheral blood samples according to the manufacturer's protocol (RNX PLUS, Yekta Tajhiz Azma, Iran). Then, RNA concentration and purity were assessed using NanoDrop 2000 UV-Vis spectrophotometer (Thermo Scientific, USA) and 1% agarose gel electrophoresis. The extracted RNA was converted into complementary DNA (cDNA), based on the manufacturer's instructions (Yekta Tajhiz Azma, Iran) using a thermocycler (Bio-rad Thermal Cycler C1000 Touch system, Germany) and kept at -20 °C until use in real-time PCR. The expression levels of the target genes were determined using a real-time PCR system (LightCycler 96 system (Roche Molecular Biochemicals, Mannheim, Germany) and SYBR Green PCR master (Ampliqon Inc., Odense, Denmark). Glyceraldehyde-3-Phosphate Dehydrogenase (GAPDH) gene was used to normalize mRNA expression levels of the target genes, including IRF4, BATF, and PU.1. Details of the designed primers are shown in Table 2. The primers' accuracy and specificity were confirmed using the Basic Local Alignment Search Tool on the US National Center for Biotechnology Information (NCBI) website (http://www.ncbi.nlm.nih.gov/tools/primer-blast/). The relative mRNA expression of each sample's target genes was calculated using the relative RNA expression quotation [25] (Table 3).

Table 1. Demographics characteristics of AR patients.

Charatristics	AR patients
Gender (M/F)	13/13
Age (years)	32.8 ± 9.1
Smoking	36 %
Asthma	4 %
Durability of illness	4 years
Self -treatment	80%
Fexofenadine	26
Fluticasone propionate	26

Fexofenadine: mg/day, Fluticasone propionate: one puff/day. F: female, M: male, Data are Mean ± SEM.

Table 2. Forward and reverse primers of target genes for real-time PCR amplification.

Gene	Forward primer	Reverse primer
IRF4	GCGGTGCGCTTTGAACAAG	AGTCCCAGTAATGGTCGCTAT
PU1	GTGCCCTATGACACGGATCTA	ACACTTTGTACGGGTCTGAG
BATF	TATTGCCGCCCAGAAGAGC	GCTTGATCTCCTTGCGTAGAG
GAPDH	CATGTACGTTGCTATCCAGGC	CTCCTTAATGTCACGCACGAT

2.3. ARIA (allergic rhinitis and its impact on asthma (classification

According to ARIA classification, AR is classified as intermittent or continuous, as well as mild or moderate/severe. Intermittent AR is defined as experiencing symptoms for <4 days in the week or <4 consecutive weeks. Persistent AR is termed as experiencing symptoms for more than four days in the week and more than 4 consecutive weeks. Mild AR is defined as not having trouble in work and school. Moderate-severe AR is defined as impairment of daily activities, sport, work, or school [26].

3. Statistical analysis

Statistical analyses were performed using the SPSS software version 24 (SPSS, Chicago, IL, USA), GraphPad Prism version 6 (GraphPad Software, La Jolla, California, USA), and Microsoft Excel 2010. The normality of the data was assessed using the Kolmogorov–Smirnov test (K–S). The gene expression levels of PU.1, IRF4, and BATF before and after one month of treatment were analyzed by T-test exam. The results were expressed as mean ± SEM and $p < 0.05$ considered statistically significant.

4. Results

4.1. Improvement in clinical symptoms of AR patients

The severity of clinical symptoms in AR patients (before and after treatment) was graded from 0 to 6 based on the ARIA classification system. The results showed that the severity of clinical symptoms in AR patients after one month of treatment with fexofenadine and fluticasone propionate significantly decreased (Table 4).

4.2. The expression levels of IRF4 and BATF genes reduced by treatment

As shown in Figure 1, the expression level of IRF4 and BATF genes significantly decreased after one month of treatment with fexofenadine and fluticasone propionate ($P < 0.001$, $P < 0.01$, respectively). These results showed that this treatment regimen could significantly affect the

Table 3. Pffafl Equation for calculating relative mRNA expression of the target genes.

$R = \frac{(E_{target})\ \Delta Ct\ \text{target}\ (\text{Control} - \text{Sample})}{(E_{Ref})\Delta Ct\ \text{Ref}\ (\text{Control} - \text{Sample})}$	
R: ratio	
E_{Target}: Efficiency of target gene	E_{Ref}: Efficiency of reference gene
ΔCt target: Ct difference of target gene before and after treatment	
ΔCt Ref: Ct difference of reference gene before and after treatment	
Control: before treatment	Sample: after treatment

Table 4. Clinical symptoms of AR patients.

Clinical symptoms	Before treatment	After treatment
Nasal rhinorrhea	5.32	0.88
Nasal Itching	3.28	0.56
Sneezing	5.2	1
Nasal Obstruction	4.16	0.48
Eye Itching	2.84	0.64
Watery eyes	2.96	0.36

Clinical symptoms are classified based on ARIA score.

Th9 cell by reducing the expression of IRF4 and BATF genes. In addition, the observed decrease in the expression levels of IRF4 and BATF genes may associate with a significant reduction in the severity of clinical symptoms in AR patients after one month of treatment (Table 4).

4.3. PU.1 gene expression levels was not affected by treatment

As shown in Figure 2, there was no significant difference in the expression levels of the PU.1 gene before and after one month of treatment with fexofenadine and fluticasone propionate in AR patients. Although this treatment regimen reduced the expression levels of IRF4 and BATF, it did not significantly affect the expression levels of the PU.1 gene.

5. Discussion

In this study, we assessed the expression levels of IRF4, BATF, and PU.1 genes in the peripheral blood cells of AR patients before and after one month of treatment with fexofenadine and fluticasone propionate. Our results showed that after one month of treatment, the expression levels of IRF4 and BATF genes decreased remarkably compared to before treatment. In contrast, the treatment had no significant effect on the expression levels of the PU.1 gene. In addition, the clinical symptoms of AR patients improved significantly compared to before treatment. Fexofenadine and fluticasone propionate are common agents in the treatment of AR, which have various effects. Fexofenadine has previously been shown to reduce nasal and ocular symptoms in AR patients [17, 27]. Fluticasone propionate improves nasal symptoms, reduces the number of nasal eosinophils, inhibits T cell function, and prevents the release of cytokines from mast cells [19, 20, 21, 22, 23]. In line with these studies, our findings indicated that fexofenadine and fluticasone propionate improve clinical symptoms in AR patients, which may be due to their effect on Th cells involved in the pathogenesis of AR such as Th9, Th17, and Th2 and/or the strengthening of regulatory T (Treg) cells, which are involved in the improvement of AR (data not shown). Besides, it may be due to a decrease in nasal eosinophils and a decrease in the release of cytokines from mast cells. However, further studies are needed to warrant.

As we implied above, our results showed a decrease in IRF4 and BATF expression levels after treatment, while this treatment did not affect PU.1 expression levels. PU.1, IRF4, and BATF transcription factors are involved in Th9 cell differentiation and IL-9 production. Although none of these can be considered the main regulators, all these factors are requisite for Th9 cell development [12, 15, 28]. Deficiency in the expression of PU.1, BATF, or IRF4 is associated with impaired Th9 development and IL-9 production [12, 15, 29, 30, 31].

It is important to note that BATF and IRF4 expression are not restricted to Th9 cells and are required for Th2 and Th17 differentiation [32, 33, 34]. BATF and IRF4 play an important role in Th2 cell development and differentiation by promoting IL-4 production and regulating GATA3 metabolism [15, 35, 36, 37]. Likewise, IRF4 and BATF are necessary for the differentiation of Th17 cells, and deletion of the IRF4 gene is associated with defects in their differentiation [38, 39]. Furthermore, Treg cells express high levels of IRF4, which is crucial for their function. For this reason, mice with the deletion of the IRF4 gene had more Treg than normal mice, while they developed autoimmune diseases [40].

Despite the role of IRF4 and BATF in regulating activity and differentiation of different Th subsets, it seems that BATF and IRF4 are expressed at higher levels in Th9 cells and play a more important role in this subpopulation [12, 15]. Regarding the role of IRF4 and BATF in the differentiation of Th9, Th2, and Th17, it seems that the reduction in clinical symptoms in AR patients treated with fexofenadine and fluticasone propionate may be due to a decrease in the population of Th9 as well as Th2 and Th17.

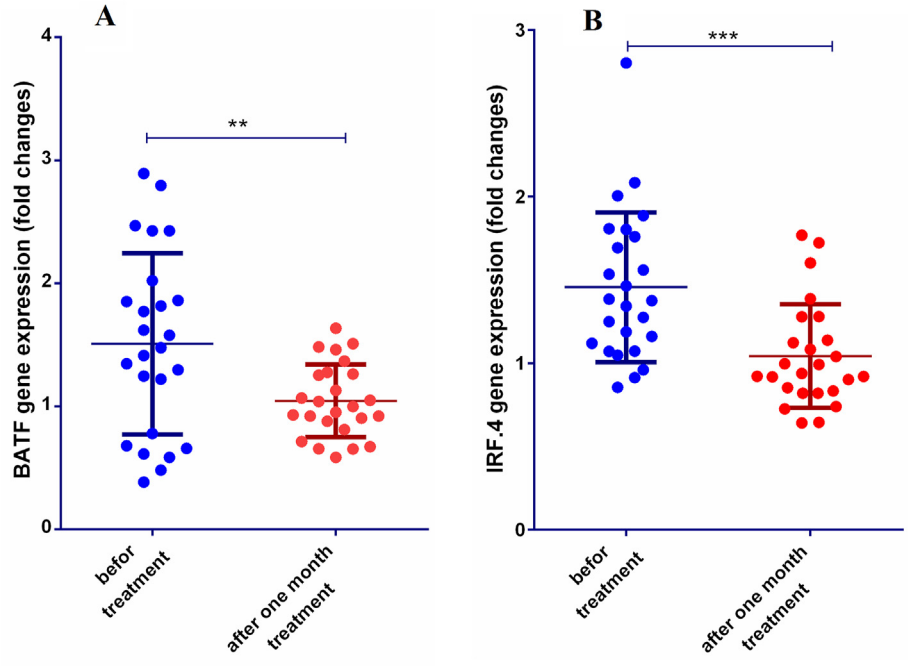

Figure 1. The effect of one month of treatment with fexofenadine and fluticasone propionate on the expression level of IRF4 and BATF genes. The expression levels of IRF4 and BATF genes were measured before and after one month of treatment with fluticasone propionate and fexofenadine by Real Time-PCR. The expression level of BATF (A) and IRF4 (B) transcription factors significantly decreased after one month of treatment compared to before treatment. (**: $P < 0.01$, ***: $P < 0.001$, respectively).

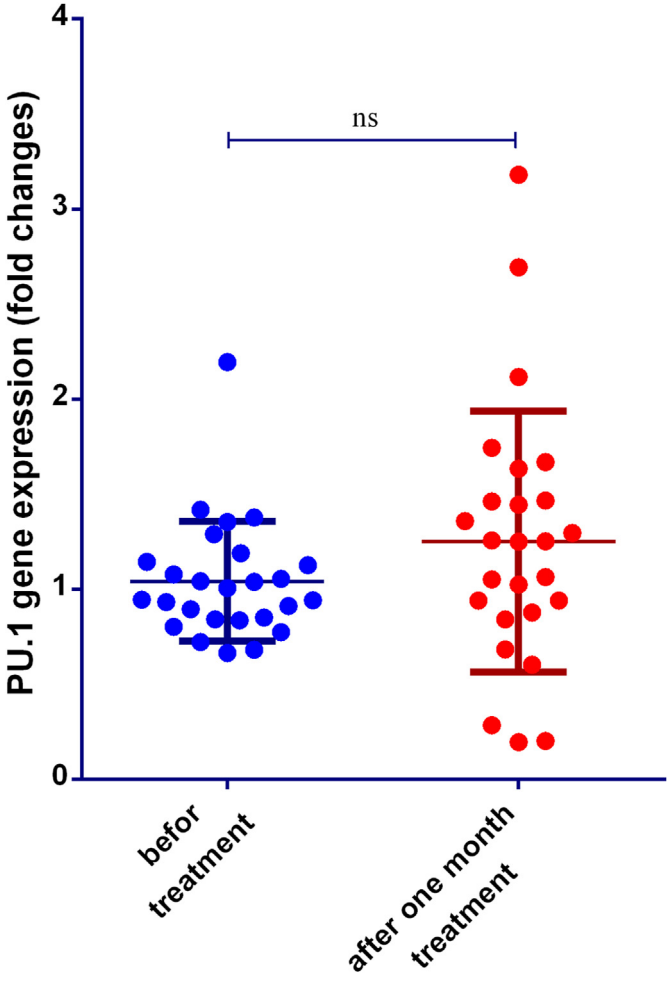

Figure 2. The effect of treatment with fexofenadine and fluticasone propionate on the gene expression level of PU.1 in AR patients. The expression levels of PU.1 gene was measured before and after one month of treatment with fexofenadine and fluticasone propionate by Real Time-PCR. No significant difference was found for the gene expression of PU.1 before and after one month of treatment. Ns: no significant.

Consistent with our findings, dexamethasone alone or in combination with vitamin D reduces the percentage of IL-9-producing cells [28]. Furthermore, it was found that BATF gene expression decreased in patients with allergic asthma treated with corticosteroids compared to untreated patients, suggesting a possible effect of corticosteroids on BATF gene expression in patients with allergic asthma [41].

Interestingly, Th9 cell contributes to the accumulation and activation of mast cells during allergic inflammation [42]. Consistent with this finding and with respect to the improvement of AR patients' clinical symptoms in the present study, fexofenadine and fluticasone propionate may also affect the accumulation of mast cells in the airway mucosa by reducing Th9 activity.

In general, the mechanisms of action of fexofenadine and fluticasone propionate in controlling the clinical symptoms of AR are not well understood and require further investigation. In this regard, the effects of fexofenadine and fluticasone propionate on other cells involved in AR development, including Th2, Th17 and, Treg cells, should be further studied.

6. Conclusion

Overall, the results of our study suggest that one month of treatment with fexofenadine and fluticasone propionate is effective in reducing the expression of IRF4 and BATF genes. Decreased expression of these two factors may improve the clinical signs of AR by reducing the activity of Th9 cells and other AR-promoting cells as well as increasing the activity of AR-controlling cells.

Declarations

Author contribution statement

Ali asghar Askari:Performed the experiments; Wrote the paper.
Parisa Feizollahi: Performed the experiments; Wrote the paper.
Alireza Rezaiemanesh: Analyzed and interpreted the data; Wrote the paper.
Farhad Salari: Analyzed and interpreted the data; Wrote the paper.
Ali Gorgin Karaji: Conceived and designed the experiments; Wrote the paper.

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Data availability statement

The data that has been used is confidential.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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