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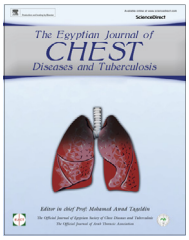

ORIGINAL ARTICLE

Serum levels of Interleukin-33 and its soluble receptor ST2 in asthmatic patients

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KEYWORDS

Interleukin-33;
Soluble ST2;
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Abstract Interleukin-33 is a member of IL-1 family of cytokines and binds to two receptors: ST2 (IL-1-R1) and IL-1 receptor accessory protein (IL-1RAP). There are two isoforms of ST2 proteins: ST2L, a transmembrane form, and a soluble ST2 (sST2), a secreted form, that can serve as a decoy receptor of IL-33. The IL-33/ST2 signaling pathway activates airway eosinophils that exacerbate airway inflammation.

The aim of this study was to analyze the serum level of IL-33 and its receptor sST2 in patients with bronchial asthma to assess if the serum level of IL-33 and/or sST2 may be a marker of the disease severity and potential therapeutic targets.

Patients and methods: This study was carried out at the Microbiology & Immunology and Chest departements, Faculty of Medicine, Zagazig University Hospitals during the period from December 2012 to September 2013. The study included 30 patients diagnosed as bronchial asthma according to GINA 2012. Patients were classified into two groups: Group I: included 15 patients 8 males and 7 females with a mean age 36.2 ± 15.8 during exacerbation of bronchial asthma. Group 2: included 15 patients 8 male and 7 female with mean age 37.3 ± 12.8. They were stable asthmatic patients and the last exacerbation was one month ago. There were 30 normal healthy persons as a control group. All patients were subjected to, full medical history, general and local examination, Plain chest X-ray PA and lateral views, pulmonary function tests, Liver and kidney function tests, intradermal skin test, skin prick test, measurement of serum levels of IL-33 (WEKA MED), IL-33 Receptor (soluble

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ST2) (OmniKine) and total IgE (IMMUNOSPEC) by enzyme linked immunosorbent technique using commercial kits.

Results: There was a highly significant increase in the serum level of IL-33 in both groups of patients ($p1 < 0.001$) with the highest level 960 ± 336 ng/ml in group 1 followed by 732.2 ± 68.3 ng/ml in group 2 while the normal control group serum level was 174 ± 41 ng/ml. As regards serum level of sST2, there was a highly significant increase in its level in both groups of patients ($p1 < 0.001$) with the highest level 96.8 ± 25 μg/ml in group 1 followed by 83.3 ± 5.3 μg/ml in group 2 while the normal control group serum level was 33.9 ± 9.6 μg/ml. In acute exacerbated patients there was significant −ve correlation between FEV1 and serum level of both total IgE and IL-33 and in stable asthmatic patients there was high significant +ve correlation between PEFR variability and serum level of sST2.

Conclusion: The serum levels of IL-33 and its receptor sST2 were markedly elevated in patients with bronchial asthma and this supports the concept of sST_2 and Interleukin-33 as a therapeutic target in asthma.

Introduction

Bronchial asthma is thought to be T helper 2 (Th2) cell-mediated immune diseases. Th2 cells produce cytokines, such as interleukin (IL)-33 which is also a chemoattractant for human Th2 cells. IL-33 is produced by mast cells after immunoglobulin (Ig) E-mediated activation and is able to trigger mast cells to release proinflammatory cytokines *in vitro* [1]. IL-33 is a member of the IL-1 family of cytokines and binds to two receptors: ST2 (IL-1R1) and IL-1 receptor accessory protein (IL-1RAP). There are two isoforms of ST2 proteins: ST2L, a transmembrane form, and soluble ST2 (sST2), a secreted form that can serve as a decoy receptor of IL-33. ST2 is highly expressed on mast cells and selectively on Th2 cells [2].

High levels of sST2 have been found in the sera of adults and children with acute asthma [3].

The IL-33/ST2 signaling pathway activates airway eosinophils that exacerbate airway inflammation. This pathway is critical for the progression of IgE-dependent inflammation. Mutations in the gene for IL1RL1 (ST2) have been linked to atopic dermatitis and asthma [4]. Steroids and combination therapies with long-acting β-agonists are the mainstay of asthma treatment and effectively suppress cytokine expression and acute inflammatory symptoms. However, they do not prevent, reverse or treat the underlying causes of disease. These treatments require constant monitoring and are associated with side-effects and resistance. Therefore, there is an urgent need for new and more effective treatments and cytokines have been extensively investigated as potential therapeutic targets. So the aim of this study was to analyze the serum level of IL-33 and its receptor sST2 in patients with bronchial asthma to assess if the serum level of IL-33 and/or sST2 may be a marker of the disease severity and potential therapeutic targets.

Patients and methods

This study was carried out at the Microbiology & Immunology and Chest Departments, Faculty of Medicine, Zagazig University Hospitals during the period from November 2012 to November 2013.The study included 30 patients with mean age 36.7 ± 14.2 diagnosed as bronchial asthma according to GINA 2012 [5] as follows:

- Recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning.
- Pulmonary function test demonstrating reversible airway obstruction, manifested by post bronchodilator increase in FEV1 > 15%.
- Peak expiratory flow (PEF): variability by 7–20%.

Patients were classified to two groups:

- Group I (asthmatic patients during acute exacerbations):

This group included 15 patients; 8 males and 7 females with a mean age 36.2 ± 15.8, during exacerbation of bronchial asthma.

The severity of exacerbations was assessed according to GINA (2012) [5], as mild, moderate, severe and respiratory arrest imminent.

- Group 2 (stable asthmatic patients):

This group included 15 patients 8 males and 7 females with mean age 37.3 ± 12.8. They were stable asthmatic patients and the last exacerbation was one month ago. They were classified according to GINA 2012 into: controlled, partially controlled and uncontrolled.

- Control group:

There were 30 normal healthy persons as a control group they were 15 males and 15 females with mean age 34.5 ± 9.

All patients were subjected to full medical history, general and local examination, Plain chest X-ray PA and lateral views, pulmonary function tests, Liver and kidney function tests and eosinophilic count. Measurement of serum levels of IL-33, sST2 and total IgE and commercial enzyme-linked immunosorbent assays were used to measure serum levels of IL-33 (WKEA MED), sST2 (OmniKine) and total IgE (IMMUNOSPEC). The assays were performed using the protocols recommended by the manufacturers.

Statistical analysis

Statistical analysis was performed with SPSS version19 software package (SPSS, Inc. Chicago). Categorical variables were