Prospective Open-Label Study of 48-Week Subcutaneous Administration of Mepolizumab in Japanese Patients with Severe Eosinophilic Asthma

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Brief running title: Mepolizumab open-label study in asthma

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Abstract

Background: Long-term efficacy and safety of mepolizumab in patients with severe eosinophilic asthma has been evaluated by large-scale double-blinded placebo control studies. However, a prospective open-label study of a long-term subcutaneous administration of mepolizumab in Japanese patients with severe eosinophilic asthma has not been reported.

Methods: This study was a prospective, 48-week, open-label trial in 32 Japanese patients with severe eosinophilic asthma who received subcutaneous administration of 100 mg mepolizumab every 4 weeks. Nine patients required daily use of oral corticosteroid despite the use of high-dose inhaled corticosteroid. Six patients with aspirin-exacerbated respiratory disease were involved.

Results: No patients failed to be continued mepolizumab administration for an entire trial period. All patients experienced no adverse events during the treatment. None of the patients experienced asthma exacerbations during an entire period. In fact, forced expiratory volume in one second was increased significantly at 24 week ($p < 0.01$) and at 48 week ($p < 0.05$). Number of eosinophils in peripheral blood was reduced after the first administration of mepolizumab in all patients, which was continued until 48 weeks with mepolizumab administration. After the start of mepolizumab administration, all of oral corticosteroid-dependent asthmatics successfully withdrew from the use of corticosteroid without exacerbations in parallel with sustained reduction in peripheral blood eosinophil count. Blood levels of thymus and activation-regulated chemokine and IgE were not changed with 48-week administration of mepolizumab.

Conclusion: This first prospective open-label pilot study in Japan showed a long-term efficacy and safety of mepolizumab in patients with severe eosinophilic asthma.

Key Words: Anti-IL-5 antibody, Eosinophilic asthma, Mepolizumab, Prospective open-label study, Thymus and activation-regulated chemokine

Resumen

Antecedentes: La eficacia y seguridad a largo plazo de mepolizumab se ha evaluado mediante grandes estudios doble-ciego controlados con placebo. Sin embargo, no hay estudios prospectivos abiertos a largo plazo que analicen la administración de mepolizumab en pacientes japoneses con asma eosinofílica grave.

Métodos: Es un estudio prospectivo, abierto, de 48 semanas de duración en 32 pacientes japoneses con asma eosinofílica grave y que recibieron la administración subcutánea de 100 mg de mepolizumab cada 4 semanas. Nueve pacientes necesitaban esteroides orales a diario a pesar del uso de altas dosis de corticoides inhalados. Seis pacientes tenían intolerancia respiratoria a aspirina.

Resultados: Ningún paciente fue retirado del estudio ni tuvo efectos adversos durante el tratamiento. Ningún paciente tuvo exacerbaciones asmáticas durante el periodo del estudio. El volumen expirado máximo en el primer segundo aumentó de forma significativa en la semana 24 ($p < 0.01$) y en la semana 48 ($p < 0.05$). El número de eosinófilos en sangre periférica se redujo tras la primera administración de mepolizumab en todos los pacientes y continuó hasta la semana 48. Después del comienzo de la administración de mepolizumab a todos los pacientes con necesidad de esteroides orales se les retiraron sin que tuvieran posteriormente exacerbaciones y en paralelo a la disminución de eosinófilos en sangre periférica. Los niveles séricos de la quemoquina tímica de regulación y activación ni de IgE cambiaron en las 48 semanas del estudio.

Conclusión: es el primer estudio piloto abierto y a largo plazo realizado en Japón que muestra la eficacia y seguridad de mepolizumab en pacientes con asma eosinofílica grave

Palabras clave: Anticuerpo anti-IL5, asma eosinofílica, mepolizumab, estudio prospectivo abierto, quemoquina tímica de regulación y activación.

Introduction

Eosinophils are important effector cells in bronchial asthma [1]. Over-expression of interleukin-5 (IL-5) has been shown in patients with a variety of eosinophil-associated disorders including bronchial asthma [2]. Mepolizumab is a humanized IgG_1 monoclonal antibody that blocks human IL-5 from binding to the IL-5 receptor [3]. It was the first biological anti-IL-5 drug tested in randomized clinical trials on bronchial asthma, although it did not inhibit biphasic asthmatic response and airway hyper-responsiveness in an antigen inhalation study [4]. In subsequent clinical studies focusing on blood eosinophil count have shown that mepolizumab was an effective treatment that reduced the risk of asthma exacerbations in patients with severe eosinophilic asthma based on the measurements of patients' symptom scores and lung function [5,6].

No gold standard test is currently available to evaluate a systemic control of asthma. Asthma Control Test (ACT) validity [7] is often used for assessment of asthma control. In fact, patients' symptom scores were significantly improved with mepolizumab in multicentre, double-blinded, placebo-controlled trials [5,6].

On the other hand, effects of mepolizumab on forced expiratory volume in one second (FEV_1) have been reported contradictory. Namely, some studies indicated a modest increase in FEV_1 with mepolizumab [6,8], whereas others showed that FEV_1 was not improved with the administration [4,5,9,10]. One reason for the discrepancy may be due to patients' severity in the studies. In fact, one study evaluated safety and efficacy of mepolizumab in patients receiving with medium-dose of inhaled corticosteroids [9].

In November 2015, the US Food and Drug Administration (FDA) committee approved mepolizumab for use in patients older 18 years with severe eosinophilic asthma at the dose of 100 mg to be administered subcutaneously once every 4 weeks [11], and in December 2015, the European Medicines Agency (EMA) approved a marketing authorization valid throughout the European Union as medicine under additional monitoring [12]. In June 2016, mepolizumab has launched in Japan for use in patients older 12 years with severe eosinophilic asthma.

Only one paper has been reported about a clinical efficacy and safety of mepolizumab in Japanese patients [13], which was a sub-analysis of the Japanese patients (N = 50) in global randomized, double-blinded, double-dummy 32-week Mepolizumab Adjunctive Therapy in Subjects with Severe Uncontrolled Refractory Asthma (MENSA) trial [6]. COSMOS was a 52-week, open-label extension study in patients who received mepolizumab or placebo in MENSA or Steroid Reduction with Mepolizumab Study (SIRIUS). [14]. This is the first prospective open-label pilot study of 48-week subcutaneous administration of mepolizumab in Japanese patients with severe eosinophilic asthma treated with high-dose inhaled corticosteroid/long-acting β_2 agonist inhalers. The primary objective of this study was to investigate whether our results may be consistent with the results in large-scale double-blinded placebo control studies. In addition, we measured blood levels of thymus and activation-regulated chemokine (TARC) as a possible candidate for a specific biomarker for the treatment of mepolizumab in severe eosinophilic asthma.

Patients and methods

Patients

Patients comprised 32 subjects (16 each in male and female), median age 68.0 years in the age range 27 - 87 years in males, and median age 57.9 years in the age range 39-80 years in females, respectively. The diagnosis of bronchial asthma was confirmed using the Global Initiative for Asthma (GINA) guidelines [15]. Enrolled patients in this study were required to have received a clinical diagnosis of bronchial asthma by experienced pulmonologists. All patients showed FEV_1 measured with a spirometer was less than 80% of the predicted value for age, sex, and height with documented short-acting β_2 agonist reversibility of > 12 % after administration of 180 µg of albuterol (salbutamol). Nine patients (3 males and 6 females) had at least 6 months history of maintenance treatment with oral corticosteroids (5 to 10 mg per day of prednisone or its equivalent) before entering the study. Six patients (3 each in male and female) were aspirin-exacerbated respiratory disease (AERD), so-called aspirin-intolerant asthma, diagnosed as reported [16]. Clinical characteristics of the patients are shown in Table 1.

All patients had to have at least two asthma exacerbations in the previous year that were treated with systemic corticosteroids, administered intravenously or orally for more than 3 days, or emergency department visit and/or hospitalization. They were receiving treatment with an inhaled corticosteroid at high-dosage of more than 500 µg fluticasone dry powder or equivalent daily dosage/long-acting β_2 agonists inhalers with an additional controller for 12 months before enrollment. In addition, all patients had to have an eosinophil count at least 150 cells/µl in blood at screening or at least 300 cells/µl at some

time during the previous year. Patients were allowed to continue their current antiasthma therapy throughout the study. Exclusion criteria included present smoking, a greater than 10 pack-year past history of smoking, parasitic infection in the 6 months before study entry, substantial uncontrolled co-morbidity, possibility of pregnancy, and history of poor treatment adherence.

Mepolizumab 100 mg was administered subcutaneously at baseline (visit 1; week 0), and then every 4 weeks for a total 44 weeks, as an add-on to appropriate standard care that could be adjusted at the physician's discretion. Thirteen visits were completed to 48 weeks. Assessment for exacerbations occurred at every 4 weeks clinic visit from baseline to 48 week (exit visit).

Safety was evaluated on each visit by assessment of adverse events, vital signs and electrocardiographic findings along with clinical laboratory testing variables at baseline (week 0) and at weeks 24 and 48. Blood eosinophil count was assessed from baseline and every 4 weeks until 48 week. FEV_1 was measured at baseline and at weeks 24 and 48 (exit visit).

This study was performed in accordance with the Good Clinical Practice guidelines, the ethics principles outlined in the Declaration of Helsinki 2008, in accordance with the Institutional Ethics Committee of the Sutoh Hospital (IRB#20160049). Written informed consent was obtained from each individual before the study commenced. This study was conducted between June 2016 and January 2018.

Clinical measurements

The percentages of predicted FEV_1 were measured, using a spirometer (FUKUDA-77, Fukuda Denshi, Tokyo, Japan), and the best of three expirations was recorded. The predicted values of FEV_1 were calculated from published equations [17,18]. Counting the number of eosinophils in peripheral blood was performed automatically by the Beckman Coulter counter (Beckman Coulter, Fullerton, CA, USA) and MAXM A/L system (Beckman Coulter). Serum levels of total immunoglobulin E (IgE) were measured by the CAP system (Phadia, Uppsala, Sweden), and plasma concentration of TARC by an enzyme-linked immunosorbent assay kit (R&D Systems, Minneapolis, MN, USA) as reported [19].

Statistical analysis

Data are presented as mean ± SD or numbers of observations, unless stated otherwise. Difference in study variables over time was analyzed by Dunnett's multiple comparison test. All statistical analyses were performed Microsoft Excel for Mac 2011. A p value < 0.05 was considered significant.

Results

The primary outcome showed that no patients failed to continue the treatment of mepolizumab because of experience of adverse events, such as local injection site reactions

and anaphylactic reactions. No patients complained of headache and signs of

nasopharyngitis. No clinically relevant trends were observed in vital signs,

electrocardiographic findings, or clinical laboratory testing data. Secondary, all patients

continued to be administered with mepolizumab for an entire trial period without a

prevalence of severe asthma exacerbations, defined as a worsening of asthma requiring

systemic corticosteroids administered intravenously or orally or emergency department

visit and/or hospitalization. FEV_1 at 24 week and at 48 week was 72.7 ± 10.0 (mean $\pm$

SD) % and 72.3 ± 9.1 % respectively, and it was increased significantly compared with

69.4 ± 11.8 % at baseline ($p < 0.01$ at week 24 and $p < 0.05$ at week 48, respectively)

(Figure 1). Other measurements indicated that blood eosinophil counts showed a rapid (at

week 4), and sustained reduction ($p < 0.01$) with 48-week administration of mepolizumab

(Figure 2). In the present study, 9 patients required daily oral corticosteroid before starting

the trail, and all of the patients successfully withdrew from daily use of oral corticosteroid

without exacerbations in parallel with sustained reduction in peripheral blood eosinophil

count after start of the therapy with mepolizumab (Figure 3). On the other hand, no changes

were observed in peripheral blood levels of TARC and IgE with 48-week administration of

mepolizumab (Figures 4 and 5).

Discussion

This was the first open-label long-term pilot study of subcutaneous administration of

mepolizumab in Japanese patients with severe eosinophilic asthma. In 32 patients treated

with high-dose inhaled corticosteroid/long-acting β_2 agonist inhalers with or without oral corticosteroid for asthma control, no patients experienced exacerbations during 48-week administration of mepolizumab. In fact, a significant increase in FEV_1 was observed at weeks 24 and 48. So, after 48 weeks, all of the patients were followed with mepolizumab administration in good controls.

ACT validity [7] is often used for assessment of asthma control. However, it mainly depends on patient's reported outcome, and furthermore the presence of rhinitis heavily affects the patient's perception of asthma control [20,21]. Some studies showed an evidence that rhinitis was associated with an incremental adverse impact on the disease-specific quality of life in asthmatic patients [20]. As a presence of rhinitis may affect the patient's perception of asthma, it has recently been suggested that ACT accuracy has not been systematically evaluated [22]. In 2015, the UK National Institute for Health and Care Excellence (NICE) has issued a draft guideline to use spirometry first to improve diagnosis of asthma [23]. Although, the guidelines say spirometry should be used as the first line investigation for asthma, and asthma should not be followed up on the basis of any single diagnostic test.

A very recent review described that blood eosinophil counts evoked as a predictive biomarker for the efficacy of treatment with mepolizumab in patients with severe eosinophilic bronchial asthma [24]. So, as the second endpoint, peripheral blood eosinophil counts were assessed in this study. The results showed that following mepolizumab administration, a rapid and pronounced reduction in peripheral blood eosinophil levels was observed in all patients, which was consistent with previous studies [4,5,9,24].

Next end point was an evaluation of the steroid-sparing effect of mepolizumab because 9 patients required daily use of oral corticosteroid before the start of mepolizumab administration in this study. All of the patients successfully withdrew from daily use of oral corticosteroid without exacerbations with mepolizumab administration in parallel with sustained reduction in peripheral blood eosinophil count, which was consistent with the results of a previous report [25].

There has been a growing interest in the identification of other biomarkers useful in the management of bronchial asthma. Frequently used option is a fractional exhaled nitric oxide (FeNO), which levels have been reported to have a close correlation with airway eosinophils [26]. However, data are still controversial [27], and a very recent paper indicated that FeNo measurement is not essential for asthma screening [28]. In fact, no significant differences of FeNO values were detected in the Dose Ranging Efficacy and Safety with Mepolizumab (DREAM) trial [5], indicating FeNO is not a specific molecular biomarker for the treatment with mepolizumab.

Bronchial asthma is a chronic inflammation of the airways, particularly with inflammation of eosinophils and T cells. $CD4^+$ Th2 cells produce cytokines such as IL-4, Il-5 and IL-13, which induce IgE production and eosinophil activation. TARC has been identified as a specific ligand for CC chemokine receptor (CCR) 4, and was shown to induce chemotaxis of $CD4^+$ Th2 cells [29], suggesting possible involvement of TARC in the pathogenesis of bronchial asthma. In fact, increased levels of TARC in peripheral blood and sputum of asthmatics has been reported [19,30,31]. In addition, it has been reported that corticosteroid treatment decreased plasma TARC levels in asthmatics [19], and decreased bronchial epithelial TARC expression which was associated with a reduction in

eosinphils and CD4^{+} Th2 cells infiltration in asthma [32], suggesting that TARC may be a useful marker of bronchial asthma. However to our knowledge, there has been no report studied about the effect of mepolizumab on plasma TARC levels. Therefore, as the last end point of this study, we first investigated the effects of mepolizumab on peripheral blood levels of TARC as well as total IgE. Nevertheless, blood levels of TARC and total IgE were not changed with 48-week administrations of mepolizumab, indicating blood levels of TARC and total IgE were not able to discriminate eosinophilic from non-eosinophilic asthma. Interestingly, a very recent paper of dupilumab, a fully human anti-IL-4 receptor α monoclonal antibody that blocks both IL-4 and IL-13 signaling, in moderate to severe uncontrolled asthma patients showed that patients who received dupilumab had greater reductions from baseline in peripheral blood levels of TARC and total IgE than did patients who received matched placebo [33].

An increasing interest has focused on serum periostin as a useful biomarker, however it has been shown periostin did not correlate with sputum eosinophilia and eosinophilic airway inflammation [34]. In one study, serum free IL-5 was measured in asthma patients treated with mepolizumab, but was non-quantifiable at baseline in most patients [35], indicating serum free IL-5 did not appear to be a useful biomarker for mepolizumab treatment. Needless to say, integrated approaches are required which involve clinical aspects, assessment of co-morbidities, functional parameters, and biomarkers of inflammation, in order to achieve the most accurate asthma control assessment and follow up.

In conclusion, our results showed a favorable long-term safety and efficacy profile of subcutaneous mepolizumab administration in Japanese patients with severe eosinophilic asthma.

Conflict of interest

The authors declare that they have no conflicts of interest.

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Table 1.   Clinical Characteristics of the Study Patients

Gender	Male	Female
Number of Patients	16	16
Age (Median)	68.0	57.9
Type: Allergic	10	8
Non-Allergic	6	8
Oral Steroid-Dependency	3	6
Aspirin Hypersensitivity (AERD)	3	3

Abbreviation: AERD, aspirin-exacerbated respiratory disease

Figure legends

Figure 1.   Change in forced expiratory volume in one second (FEV_1) before

mepolizumab therapy (0 week), and 24 week, 48 week after start of the therapy. Significant

improvement in FEV_1 was seen at 24 week and at 48 week, respectively.
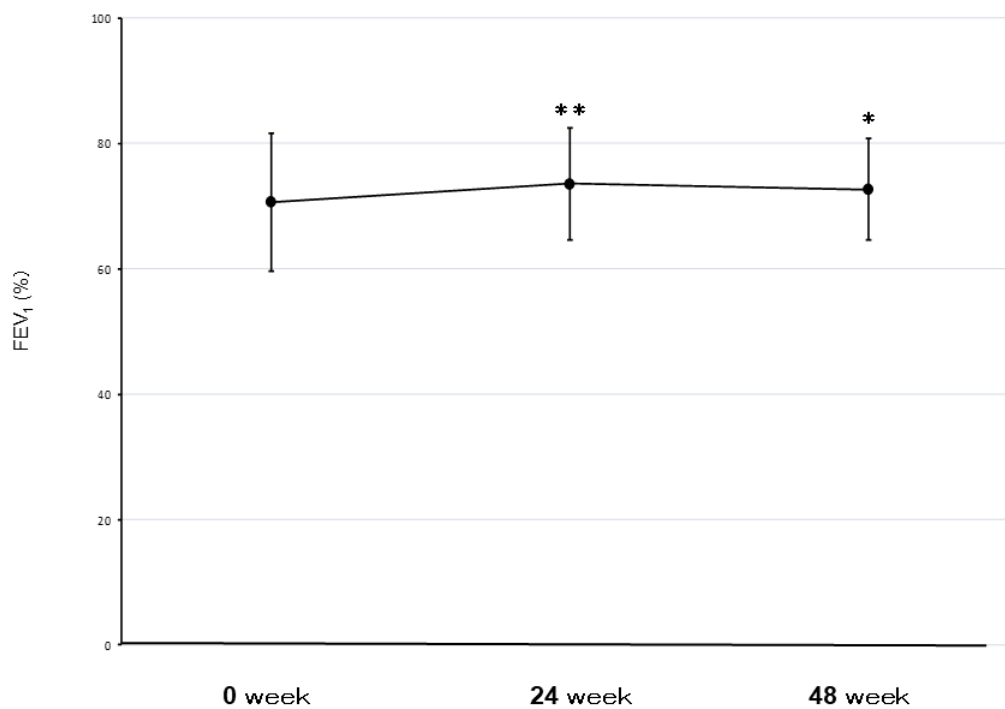
*: $p < 0.05$; **: $p < 0.01$.

Fig. 1

Figure 2.   Change in peripheral blood eosinophil count before mepolizumab therapy (0 week), and 4 week, 24 week and 48 week after start of the therapy. A rapid and sustained significant reduction in peripheral blood eosinophil count was seen at 4, 24 and 48 week, respectively. **: $p < 0.01$.
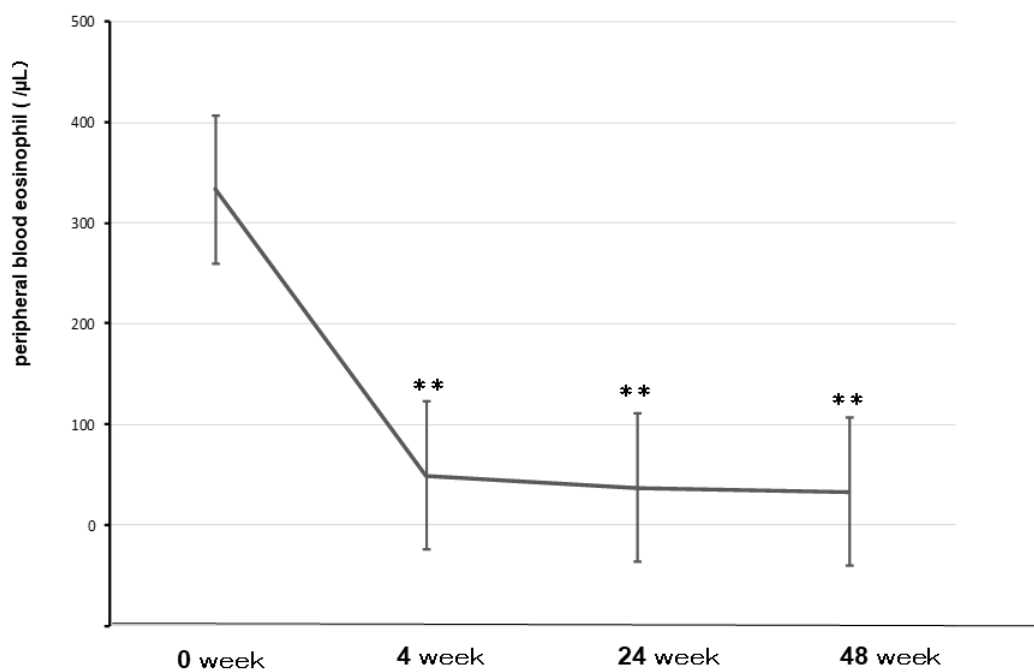
Fig. 2

Figure 3. Change in peripheral blood eosinophil count in oral corticosteroid-dependent asthma patients before mepolizumab therapy (0 week) and every 4 weeks thereafter. Solid lines show eosinophil count under corticosteroid administration, and dotted lines without corticosteroid. All of 9 corticosteroid-dependent asthma patients successfully withdrew from daily use of oral corticosteroid without exacerbations in parallel with sustained reduction in peripheral blood eosinophil count after start of the therapy.
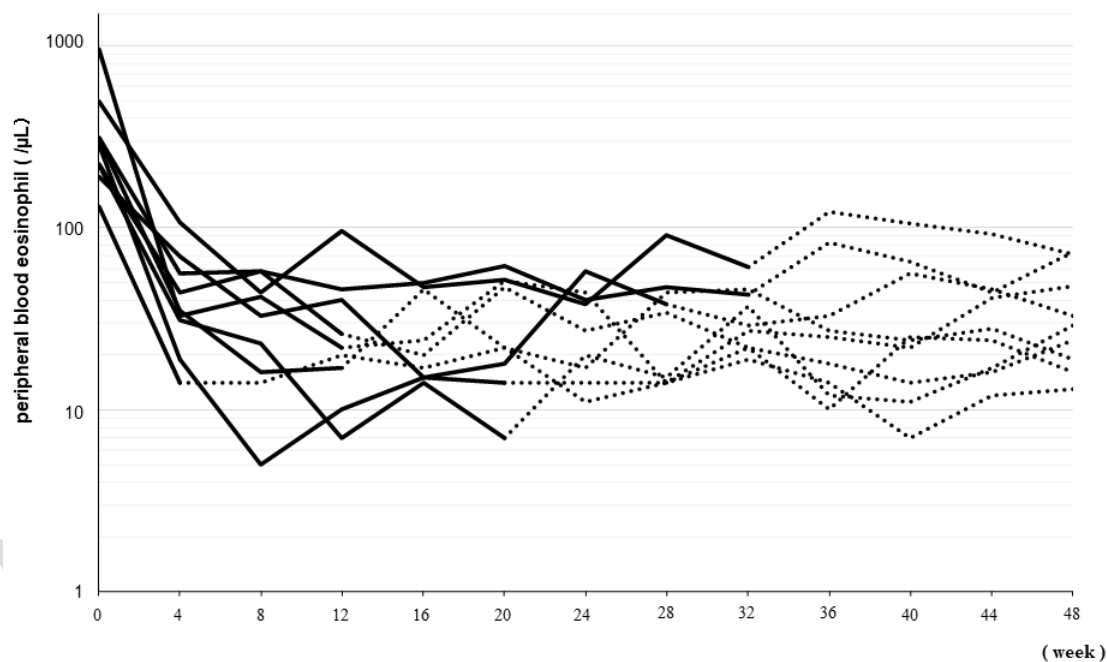
Fig. 3

Figure 4.   Change in plasma thymus and activation-regulated chemokine (TARC) levels

before mepolizumab therapy (0 week), and 24 week, 48 week after start of the therapy.

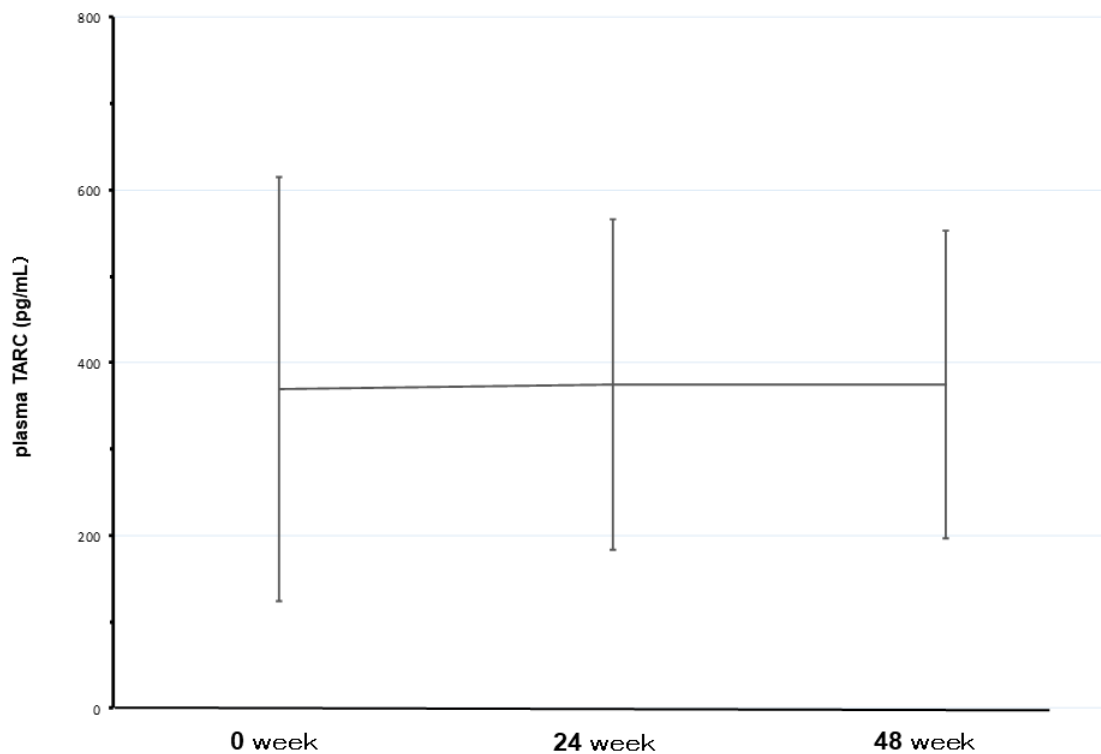Mepolizumab showed no significant effect on plasma TARC levels.

Fig. 4

Figure 5. Change in serum total IgE levels before mepolizumab therapy (0 week), and 24 week, 48 week after start of the therapy. Mepolizumab showed no significant effect on serum total IgE levels.

Fig. 5