ORIGINAL ARTICLE

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

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■ Abstract

Background: The long-term efficacy and safety of mepolizumab in patients with severe eosinophilic asthma has been evaluated in large-scale double-blind placebo-controlled trials. However, a prospective open-label trial of long-term subcutaneous administration of mepolizumab has not been performed in Japanese patients with severe eosinophilic asthma.

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

Results: All patients took mepolizumab throughout the study period. No patients experienced adverse events during the treatment. None of the patients experienced asthma exacerbations during the trial. In fact, forced expiratory volume in 1 second increased significantly at 24 weeks ($P<.01$) and at 48 weeks ($P<.05$). The peripheral blood eosinophil count in peripheral blood decreased after the first administration of mepolizumab in all patients and remained low until week 48. After starting mepolizumab, all oral corticosteroid–dependent asthmatics successfully withdrew corticosteroids without exacerbations and experienced a sustained reduction in peripheral blood eosinophil count. Blood levels of thymus and activation-regulated chemokine and IgE remained unchanged after 48 weeks of therapy with mepolizumab.

Conclusion: This first prospective open-label pilot study in Japan demonstrated the 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

Introducción: 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 major effector cells in bronchial asthma [1]. Overexpression of interleukin (IL) 5 has been demonstrated 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 or airway hyperresponsiveness in an antigen inhalation study [4]. Subsequent clinical studies focusing on blood eosinophil count and based on symptom scores and lung function showed that mepolizumab was an effective treatment that reduced the risk of asthma exacerbations in patients with severe eosinophilic asthma [5,6].

While no gold standard test is currently available to evaluate systematic control of asthma, the Asthma Control Test (ACT) [7] is often applied. In fact, symptom scores were significantly improved with mepolizumab in multicenter, double-blind, placebo-controlled trials [5,6].

Data on the effects of mepolizumab on forced expiratory volume in 1 second (FEV$_1$) are contradictory: some studies indicated a modest increase in FEV$_1$ with mepolizumab [6,8], whereas others showed that FEV$_1$ did not improve [4,5,9,10]. One reason for the discrepancy may be differences in disease severity. In fact, one study evaluated the safety and efficacy profile of mepolizumab in patients receiving medium-dose inhaled corticosteroids [9].

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

Only 1 paper has reported data on the clinical efficacy and safety of mepolizumab in Japanese patients [13]. The study was a subanalysis of 50 Japanese patients in a global randomized, double-blind, double-dummy, 32-week trial known as Mepolizumab Adjunctive Therapy in Subjects with Severe Uncontrolled Refractory Asthma (MENSA) [6]. Mepolizumab was also assessed in COSMOS, a 52-week, open-label extension study in patients who received mepolizumab or placebo in MENSA or in the Steroid Reduction with Mepolizumab Study (SIRIUS). [14]. Ours is the first prospective open-label pilot study of 48-week subcutaneous administration of mepolizumab in Japanese patients with severe eosinophilic asthma under treatment with high-dose inhaled corticosteroids/long-acting ß$_2$-agonist inhalers. The primary objective of this study was to investigate whether our results were consistent with the results of large-scale double-blind placebo-controlled studies. In addition, we measured blood levels of thymus and activation-regulated chemokine (TARC) as a potential specific biomarker for the treatment of mepolizumab in severe eosinophilic asthma.

Patients and Methods

Patients

The study population comprised 32 patients (16 men and 16 women). Median age was 68.0 years (range, 27-87 years) in men and 57.9 years (range, 39-80 years) in women. The diagnosis of bronchial asthma was confirmed based on the Global Initiative for Asthma (GINA) guidelines [15]. Patients were required to have received a clinical diagnosis of bronchial asthma by experienced pulmonologists. FEV$_1$ measured with a spirometer was less than 80% of the predicted value for age, sex, and height, with documented short-acting ß$_2$-agonist reversibility of >12% after administration of 180 µg of albuterol (salbutamol). Nine patients (3 males and 6 females) had been receiving maintenance treatment with oral corticosteroids (5 to 10 mg per day of prednisone or its equivalent) for at least 6 months before entering the study. Six patients (3 men and 3 women) had aspirin-exacerbated respiratory disease (AERD, also known as aspirin-intolerant asthma), which was diagnosed based on criteria reported elsewhere [16]. The clinical characteristics of the patients are shown in the Table.

All patients had to have experienced at least 2 asthma exacerbations in the previous year that were treated with systemic corticosteroids administered intravenously or orally for more than 3 days or that required a visit to the emergency department and/or hospitalization. They were receiving treatment with high-dose inhaled corticosteroids (>500 µg fluticasone dry powder or equivalent daily dosage/long-acting ß$_2$-agonist inhalers) with an additional controller for 12 months before enrollment. In addition, all patients had to have an eosinophil count ≥150/µL in blood at screening or ≥300/µL at some time during the previous year. Patients were allowed to continue their current antiasthma therapy throughout the study. The exclusion criteria included present smoking, a past history of smoking greater than 10 pack-years, parasitic infection in the 6 months before study entry, substantial uncontrolled comorbidity, 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 of 44 weeks as an add-on to appropriate standard care that could be adjusted at the physician's discretion. Thirteen visits were completed up to 48 weeks. Patients were asked about

Table. Clinical Characteristics of the Study Patients

Gender	Male	Female
Number of patients	16	16
Median age, y	68.0	57.9
Type: Allergic	10	8
Nonallergic	6	8
Oral corticosteroid–dependent	3	6
Aspirin hypersensitivity (AERD)	3	3

Abbreviation: AERD, aspirin-exacerbated respiratory disease.

exacerbations at every 4-week visit from baseline to week 48 (exit visit).

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

This study was performed in accordance with Good Clinical Practice guidelines and the ethics principles outlined in the Declaration of Helsinki 2008 and approved by the Institutional Ethics Committee of Sutoh Hospital (IRB#20160049). Written informed consent was obtained from each patient 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), and the best of 3 expirations was recorded. The predicted values of FEV_1 were calculated using published equations [17,18]. Eosinophils in peripheral blood were counted automatically using a counter (Beckman Coulter) and the MAXM A/L system (Beckman Coulter). Serum levels of total IgE were measured using the CAP system (Phadia), and the plasma concentration of TARC was assessed using enzyme-linked immunosorbent assay (R&D Systems), as reported elsewhere [19].

Statistical Analysis

Data are presented as mean (SD) or numbers of observations, unless stated otherwise. Differences in study variables over time were analyzed using the Dunnett multiple comparison test. All statistical analyses were performed using Microsoft Excel for Mac 2011. A P value <.05 was considered significant.

Results

No patients failed to continue treatment with mepolizumab because of adverse events, such as local injection site reactions and anaphylactic reactions. No patients complained of headache or signs of nasopharyngitis. No clinically relevant trends were observed in vital signs, electrocardiographic findings, or clinical laboratory test data. All patients continued to receive mepolizumab throughout the trial period, with no severe asthma exacerbations, defined as a worsening of asthma requiring systemic corticosteroids administered intravenously or orally or a visit to the emergency department and/or hospitalization. Mean FEV_1 at weeks 24 and 48 was 72.7% (10.0%) and 72.3% (9.1%), respectively, that is, a significant increase compared with 69.4% (11.8%) at baseline (P<.01 at week 24 and P<.05 at week 48) (Figure 1). Other measurements indicated that blood eosinophil counts showed a rapid (at week 4) and sustained reduction (P<.01) after 48 weeks of mepolizumab (Figure 2). In the present study, 9 patients required daily oral corticosteroid therapy before starting the trial, and all of the patients successfully withdrew from daily use of oral corticosteroids without exacerbations and in parallel
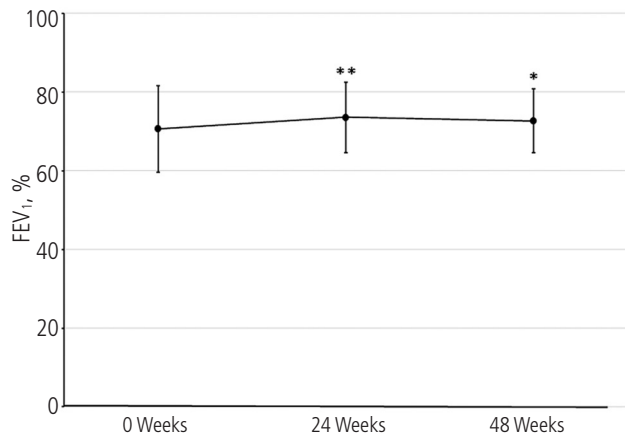

Figure 1. Change in forced expiratory volume in 1 second (FEV_1) before mepolizumab therapy (week 0) and at weeks 24 and 48 after the start of therapy. A significant improvement in FEV_1 was seen at weeks 24 and 48. *P<.05; **P<.01.
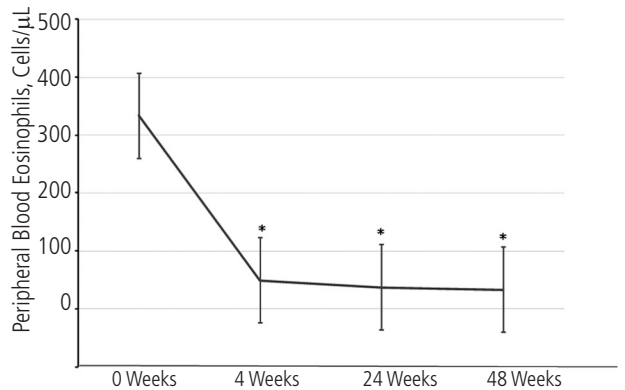

Figure 2. Change in peripheral blood eosinophil count before mepolizumab therapy (week 0) and at weeks 4, 24, and 48 after initiation of therapy. A rapid and sustained significant reduction in peripheral blood eosinophil count was seen at weeks 4, 24, and 48. *P<.01.
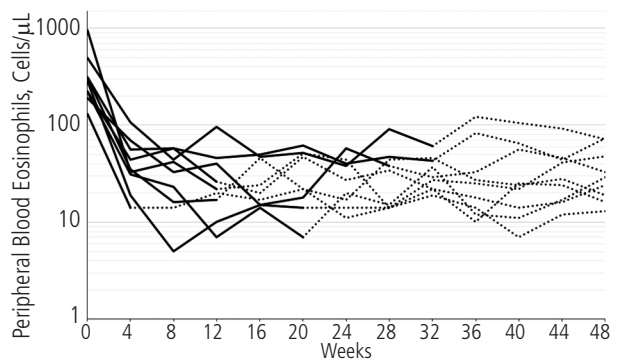

Figure 3. Change in peripheral blood eosinophil count in oral corticosteroid–dependent asthma patients before therapy with mepolizumab (week 0) and every 4 weeks thereafter. Solid lines show the eosinophil count under corticosteroid administration, and dotted lines show the eosinophil count without corticosteroids. All of 9 corticosteroid-dependent asthma patients successfully withdrew daily use of oral corticosteroids, without exacerbations and in parallel with a sustained reduction in peripheral blood eosinophil count after initiation of therapy.
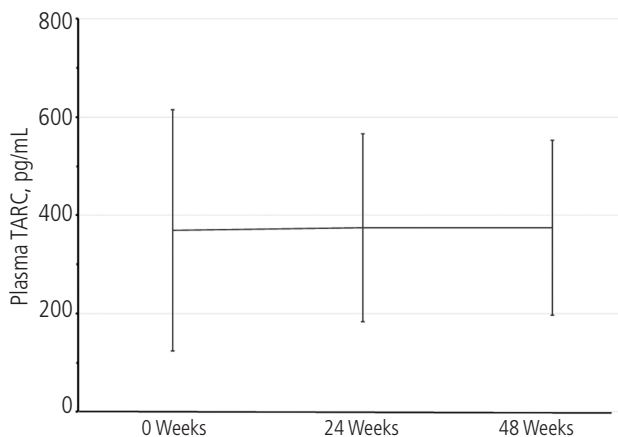
Figure 4. Change in plasma thymus and activation-regulated chemokine (TARC) levels before initiation of mepolizumab (week 0) and at weeks 24 and 48 after the start of the therapy. Mepolizumab showed no significant effect on plasma TARC levels.
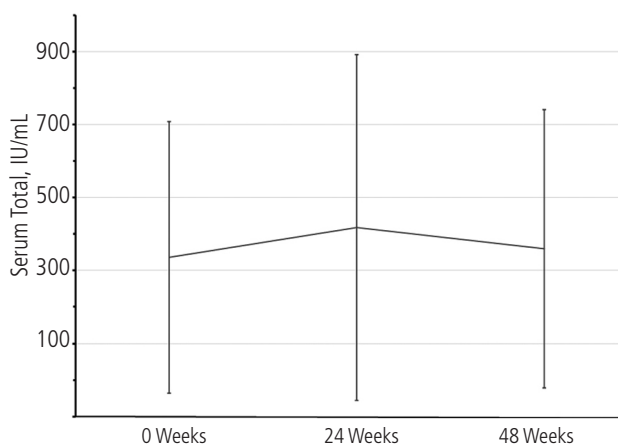

Figure 5. Change in serum total IgE levels before initiation of mepolizumab (week 0) and at weeks 24 and 48 after the start of the therapy. Mepolizumab showed no significant effect on serum total IgE levels.

with sustained reduction in peripheral blood eosinophil count after initiation of therapy (Figure 3). On the other hand, no changes were observed in peripheral blood levels of TARC and IgE after 48 weeks of mepolizumab (Figures 4 and 5).

Discussion

This was the first long-term, open-label pilot study of subcutaneous administration of mepolizumab in 32 Japanese patients with severe eosinophilic asthma treated with high-dose inhaled corticosteroids/long-acting β_2-agonists with or without oral corticosteroids. No patients experienced exacerbations during their 48-week course of mepolizumab. In fact, a significant increase in FEV_1 was observed at weeks 24 and 48. Therefore, after 48 weeks, all of the patients continued treatment with mepolizumab.

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

A recent review reported that blood eosinophil counts could be a predictive biomarker for the efficacy of treatment with mepolizumab in patients with severe eosinophilic bronchial asthma [24]. Therefore, we assessed peripheral blood eosinophil counts as our second endpoint. We observed a rapid and pronounced reduction in peripheral blood eosinophil levels in all patients after therapy with mepolizumab. This finding was consistent with data from previous studies [4,5,9,24].

We also evaluated the corticosteroid-sparing effect of mepolizumab, because 9 patients required daily use of oral corticosteroids before initiating mepolizumab. All of the patients successfully took daily oral corticosteroids without exacerbations and in parallel with a sustained reduction in peripheral blood eosinophil count, which was consistent with the results of a previous report [25].

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

Bronchial asthma is a chronic inflammation of the airways involving mainly eosinophils and T cells. CD4$^+$ T$_H$2 cells produce cytokines such as IL-4, Il-5, and IL-13, which induce production of IgE and activation of eosinophils. TARC has been identified as a specific ligand for CC chemokine receptor 4 and was shown to induce chemotaxis of CD4$^+$ T$_H$2 cells [29], suggesting possible involvement of TARC in the pathogenesis of bronchial asthma. In fact, increased levels of TARC in the peripheral blood and sputum of asthmatics has been reported [19,30,31]. In addition, corticosteroid treatment decreased plasma TARC levels in asthmatics [19]. It also decreased bronchial epithelial TARC expression, which was associated with a reduction in eosinophil counts and CD4$^+$ T$_H$2 cell infiltration in asthma [32], suggesting that TARC may be a useful marker of bronchial asthma. However, to our knowledge, there have been no reports on the effect of mepolizumab on plasma TARC levels. Therefore, as the last endpoint of this study, we investigated the effects of mepolizumab on peripheral blood levels of TARC and on total IgE. Blood levels of TARC and total IgE remained unchanged after a 48-week course

of mepolizumab, indicating that neither parameter was able to discriminate eosinophilic from noneosinophilic asthma. Interestingly, a very recent study on treatment of moderate to severe uncontrolled asthma with dupilumab, a fully human anti–IL-4 receptor α monoclonal antibody that blocks both IL-4 and IL-13 signaling, showed that patients who received dupilumab had greater reductions from baseline in peripheral blood levels of TARC and total IgE than patients who received matched placebo [33].

Serum periostin is increasingly interesting as a useful biomarker, although it did not correlate with sputum eosinophilia or eosinophilic airway inflammation [34]. In one study, serum free IL-5 was measured in asthma patients treated with mepolizumab but was not quantifiable at baseline in most patients [35], indicating that serum free IL-5 did not appear to be a useful biomarker for treatment with mepolizumab. Needless to say, integrated approaches involving clinical aspects, assessment of comorbidities, functional parameters, and biomarkers of inflammation are required in order to achieve as accurate an evaluation as possible of asthma control and follow-up.

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

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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