Switching Treatment from Mepolizumab to Benralizumab for Elderly Patients with Severe Eosinophilic Asthma: A Retrospective Observational Study

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Abstract:
Objective Switching from mepolizumab to benralizumab has been reported to significantly improve both asthma control and the lung function. However, the data on its efficacy in elderly patients with severe eosinophilic asthma are limited. This study aimed to assess whether elderly patients with severe eosinophilic asthma could experience an improved asthma control and lung function when switching directly from mepolizumab to benralizumab.

Methods In this single-center, retrospective study conducted between February 2017 and September 2018, we assessed the effect of switching the treatment directly from mepolizumab to benralizumab on eosinophil levels, exacerbation rates, and lung function. We compared the treatment responses between the two groups using either Fisher’s exact test or Mann-Whitney U-test, as appropriate.

Patients We enrolled 12 elderly patients (age ≥65 years) with severe eosinophilic asthma treated with mepolizumab at Hiroshima Prefectural Hospital (Hiroshima, Japan) during the study period. Six patients were switched from mepolizumab to benralizumab, and six continued with the mepolizumab treatment.

Results The switch from mepolizumab to benralizumab caused a near-complete reduction in the eosinophil count (p=0.008). The annual rate of clinically relevant exacerbations and hospitalizations diminished as well, albeit with no statistical significance. We found no improvement in the lung function after switching treatment and no difference in the treatment response between the groups.

Conclusion Although this study is based on a small sample of participants, the results indicate that both mepolizumab treatment and switching from mepolizumab to benralizumab treatment without a washout period have clinically relevant asthma control benefits for elderly patients with severe eosinophilic asthma.

Key words: severe asthma, anti-IL-5 monoclonal antibodies, eosinophil, interleukin-5, elderly patients

Introduction
Severe asthma is defined as asthma that is inadequately controlled by currently available standard treatments, including high-dose inhaled corticosteroids (ICSs) and long-acting β-2-adrenergic agonists (LABAs). About 5-10% of all cases of asthma are classified as severe (1, 2). A long-term complication is airway remodeling, which manifests as a progressive increase of symptoms and a corresponding decrease in bronchodilator responsiveness (3, 4). Therefore, severe asthma has been associated with a diminished health-related quality of life and high healthcare costs (1, 5).

A particularly severe asthma subtype is late-onset eosino-
phlic asthma (6, 7). Patients with this difficult-to-treat condition show eosinophilic airway inflammation despite being treated with high doses of ICSs/LABA and they are also prone to frequent and often life-threatening exacerbations (6, 8). The age of onset is higher in these patients than in patients with classical atopic asthma (6). Moreover, it is frequently undiagnosed or misdiagnosed (1) due to its atypical presentation, age-related reduction in dyspnea perception, and associated comorbidities (9, 10). Asthma and chronic obstructive pulmonary disease (COPD) can sometimes overlap and converge (9, 11), thus making the differentiation between them difficult in elderly populations (12).

The clinical recognition of this relatively rare asthma subtype has become even more important since targeted therapies, such as anti-interleukin-5 (IL-5) monoclonal antibodies, have been developed (13). Since previous studies have emphasized the importance of eosinophils in mediating exacerbations (14), the resolution of eosinophilic inflammation has been suggested to be a promising therapeutic strategy (15). IL-5 is an important cytokine for eosinophil maturation, survival, and activation (16, 17). Mepolizumab is an anti-IL-5 humanized immunoglobulin G (IgG) 1/k monoclonal antibody that significantly reduces the eosinophil count in patients with severe eosinophilic asthma in clinical trials experience a relatively fast and almost total reduction in blood eosinophils (20). These antibodies decreased the exacerbation rate, had a glucocorticoid-sparing effect, and improved asthma-related quality of life and lung function (21-27). Although benralizumab suppresses eosinophils to a greater extent than does mepolizumab, it is unclear whether this difference between the two drugs has any clinical benefit. Recently, a clinical study demonstrated that switching from mepolizumab to benralizumab in patients with an inadequate response was associated with significantly improved asthma control and lung function (28). However, the median age of the subjects was 54.0 years; hence, the clinical experience of this switch in elderly patients aged >65 years is insufficient, and its therapeutic effect still remains unclear.

We previously showed that mepolizumab effectively reduced the blood eosinophil levels, oral corticosteroids (OCS) intake, and the exacerbation rate in elderly patients with severe asthma and overlapping COPD (29). Therefore, we hypothesized that it is possible that the greater eosinophil-depleting properties of benralizumab confer superior clinical efficacy over mepolizumab in such patients. To test this hypothesis, we retrospectively evaluated the changes in asthma control and the lung function following a switch in treatment from mepolizumab to benralizumab without a washout period. Moreover, we compared the treatment response in patients who switched treatments and those who continued with the mepolizumab treatment.

Materials and Methods

Study design and patients

This retrospective study spans a period between February 2017 and September 2018. It was performed in accordance with the Declaration of Helsinki. The Ethics Committee of Hiroshima Prefectural Hospital approved the study protocol. The requirement of written patient consent was waived because this was a retrospective study, and patient anonymity was secured. The study complied with the Japanese Ethical Guidelines for Medical and Health Research involving Human Subjects (30), which do not require informed consent from patients enrolled in studies not utilizing human biological specimens. However, patients were provided the opportunity to opt out of the study, by announcing the study information on bulletin boards in the hospital.

We recruited 20 elderly patients (age >65 years) with severe eosinophilic asthma who received mepolizumab treatment at Hiroshima Prefectural Hospital between February 2017 and September 2018. The inclusion criteria are shown in Fig. 1. All patients were treated with high-dose ICSs plus at least one additional controller, as indicated in the guidelines of the European Respiratory Society/American Thoracic Society (ERS/ATS) (2). All subjects had a peripheral blood eosinophil count of at least 150 cells/μL at the start of mepolizumab treatment or at least 300 cells/μL some time during the previous year (21, 23, 24, 31). Eighteen of the 20 patients were treated with mepolizumab for at least 4 months. Six patients moved to long-term care hospitals due to a deterioration in their general health condition because of multiple comorbidities. In September 2018, physicians explained the following benefits of benralizumab treatment to the 12 patients: 1) reduced health care costs and frequency of regular treatment because benralizumab is administered every 8 weeks, and 2) the possibility of a greater improvement in the lung function and asthma control because benralizumab suppresses eosinophils to a greater extent than mepolizumab. Six patients requested to switch to benralizumab without a washout period, whereas six preferred to continue mepolizumab. We thereafter compared the patients who switched treatments (Switched group) and those who continued with the mepolizumab treatment (Mepolizumab group).

Data collection and definitions

All subjects had previously received 100 mg mepolizumab subcutaneously at 4-week intervals. The six patients who agreed to switch from mepolizumab to benralizumab were given 30 mg benralizumab subcutaneously at 4-week intervals for the first three injections and then an injection every 8 weeks. The other six patients continued to receive 100 mg mepolizumab injections every 4 weeks.

We recorded the blood eosinophil levels, frequency of ex-
Figure 1. Patient selection flow diagram. A flow diagram illustrating the process of enrolling and selecting patients with severe eosinophilic asthma for this study. ATS/ERS: The American Thoracic Society/European Respiratory Society

Statistical analysis

The data were analyzed using JMP, Version 14.1.0 (SAS Institute, Cary, USA). Categorical variables are presented as numbers (n) and percentages (%). Continuous variables are expressed as the mean ± standard error of the mean (SEM). The Steel-Dwass multiple comparison test was performed to compare treatment efficacy between each timepoint. The pre-treatment baseline characteristics of the two groups were compared using Fisher’s exact test or Mann-Whitney U-test, as appropriate. Differences with a p-value <0.05 were considered to be statistically significant.

Results

Patient characteristics

We included 12 elderly patients (six males and six females; age, 76.3±1.5 years) with severe eosinophilic asthma. The patient demographic and clinical characteristics at the start of mepolizumab administration are shown in Table. The mean age at asthma onset was 57.5±5.6 years, with a mean disease duration before mepolizumab treatment of 18.4±5.3 years. Five patients (45.5%) were former smokers. All patients were treated with ICSs/LABAs. Eight (66.7%) patients received long-acting muscarinic antagonists, and seven (58.3%) received leukotriene receptor antagonists. Two patients in the Mepolizumab group had at least a 6-month history of maintenance OCS treatments with a dose of 20 mg of prednisolone (or prednisolone equivalent). The mean duration of the previous mepolizumab treatment was 12.5±2 months. Ten patients (83.3%) responded to mepolizumab treatment when assessed after 1 year of treatment. Furthermore, nine patients (75.0%) were super-responders to mepolizumab treatment. The mean time between stopping the mepolizumab treatment and starting the benralizumab treatment was 36.7±4.2 days. There were no significant differences in the clinical characteristics at baseline between the Switched and Mepolizumab groups.
Table. Clinical Characteristics of Study Patients at Pre-treatment Baseline.

| Characteristics                                      | All patients (n=12) | Mepolizumab group (n=6) | Switched group (n=6) | p value |
|------------------------------------------------------|---------------------|-------------------------|----------------------|---------|
| Age (Years)                                          | 76.3±1.5            | 77.5±2.0                | 75.0±2.1             | 0.629   |
| Sex (Male/Female)                                    | 6/6                 | 3/3                     | 3/3                  | 1.000   |
| BMI                                                  | 22.3±1.7            | 22.8±1.6                | 21.8±3.1             | 0.298   |
| Duration of asthma (years)                           | 18.4±5.3            | 20.8±11.0               | 16.3±4.7             | 1.000   |
| Number of mepolizumab injections until 09/2018       | 13.1±1.9            | 13.2±0.9                | 13.2±4.0             | 1.000   |
| Mepolizumab responder (Yes/No)                       | 10/2                | 5/1                     | 5/1                  | 1.000   |
| Smoking history                                      |                     |                         |                      |         |
| Current/Former/Never                                 | 0/6/6               | 0/3/3                   | 0/3/3                | 1.000   |
| Pack-years                                           | 14.7±5.2            | 11.0±5.6                | 18.3±9.0             | 0.733   |
| Current medical condition                            |                     |                         |                      |         |
| Any comorbidity (Yes/No)                             | 10/2                | 6/0                     | 4/2                  | 0.455   |
| Allergic rhinitis (Yes/No)                           | 5/7                 | 2/4                     | 3/3                  | 1.000   |
| Atopic dermatitis (Yes/No)                           | 1/11                | 1/5                     | 0/6                  | 1.000   |
| Eosinophilic chronic rhinosinusitis with nasal polyposis (Yes/No) | 4/8                 | 2/4                     | 2/4                  | 1.000   |
| Osteoporosis (Yes/No)                                | 1/11                | 1/5                     | 0/6                  | 1.000   |
| Diabetes mellitus (Yes/No)                           | 4/8                 | 2/4                     | 2/4                  | 1.000   |
| Chronic heart failure (Yes/No)                       | 2/10                | 1/5                     | 1/5                  | 1.000   |
| Other comorbidities (Yes/No)                         | 2/10                | 2/4                     | 0/6                  | 0.455   |
| Clinically significant exacerbations (/year)          | 1.8±0.6             | 1.9±1.0                 | 1.6±0.9              | 0.807   |
| Exacerbations requiring hospitalization (/year)       | 1.4±0.6             | 1.9±1.0                 | 0.9±0.8              | 0.267   |
| Blood test                                           |                     |                         |                      |         |
| Eo (%): historical                                   | 11.7±1.7            | 10.5±2.4                | 12.8±2.5             | 1.000   |
| Eo (%): at baseline                                  | 7.5±1.9             | 5.6±2.0                 | 9.5±3.3              | 0.575   |
| Eo (cells/µL): historical                            | 898.7±224.8         | 713.3±192.1             | 1,084.1±414.4        | 0.630   |
| Eo (cells/µL): at baseline                           | 601.9±240.4         | 337.7±101.3             | 866.1±465.0          | 0.298   |
| IgE (U/mL): at baseline                              | 2,555.6±1,960.2     | 4,510.8±3,910.2         | 600.3±296.1          | 0.810   |
| Spirometry                                           |                     |                         |                      |         |
| FVC (L)                                              | 2.18±0.15           | 2.30±0.19               | 2.05±0.23            | 0.379   |
| FEV1 before bronchodilation (L)                       | 1.05±0.08           | 1.14±0.14               | 0.96±0.09            | 0.810   |
| FEV1 before bronchodilation (% of predicted)         | 61.0±5.8            | 69.4±7.3                | 52.6±8.6             | 0.230   |
| FEV1/FVC ratio before bronchodilation                | 50.7±3.5            | 54.2±3.7                | 47.1±6.0             | 0.471   |
| Medication                                           |                     |                         |                      |         |
| ICS+LABA (Yes/No)                                    | 12/0                | 6/0                     | 6/0                  | 1.000   |
| ICS+LABA+LAMA (Yes/No)                               | 8/4                 | 4/2                     | 4/2                  | 1.000   |
| LTRA (Yes/No)                                        | 7/5                 | 4/2                     | 3/3                  | 1.000   |
| OCS (Yes/No)                                         | 2/10                | 2/4                     | 0/6                  | 0.455   |
| OCS dose (mg)                                        | 20.0±0.0            | 20.0±0.0                | 0.0±0.0              | 0.174   |

Data are presented as means±standard error of the mean (SEM).

The p values are derived from comparisons between the Mepolizumab and Switched groups.

BMI: body mass index, COPD: chronic obstructive pulmonary disease, Eo: eosinophils, FVC: forced vital capacity, FEV1: forced expiratory volume in 1 second, ICS: inhaled corticosteroids, IgE: immunoglobulin E, LABA: long-acting beta-agonist, LAMA: long-acting muscarinic antagonist, LTRA: leukotriene receptor antagonist, OCS: oral corticosteroids

Clinical parameters under mepolizumab and benralizumab treatments

Comparisons between the three timepoints in each group are shown in Figs. 2-4.

Blood eosinophils

The blood eosinophil level in the Switched group decreased from 866.1±465.0 cells/µL at pre-treatment baseline to 121.9±79.6 cells/µL at pre-benralizumab baseline (p=0.156; Fig. 2A). The switch from mepolizumab to benralizumab reduced the blood eosinophil level to below the detection level (p=0.008; Fig. 2A). The mepolizumab group showed a trend toward decreasing blood eosinophil levels from 337.7±101.3 cells/µL at the pre-treatment baseline to 94.2±63.8 cells/µL 1 year later (p=0.077; Fig. 2B). We found no significant difference in the blood eosinophil levels after 1 year and 2 years of mepolizumab treatment (94.2±63.8 vs. 69.5±25.7 cells/µL, respectively; p=0.751; Fig. 2B). Although statistically insignificant, mepolizumab seems to have influenced the decrease in blood eosinophils during the study period (p=0.156; Fig. 2B).

Exacerbation rates and OCS use

We found the annual clinically significant exacerbation rates to decrease during the treatment with mepolizumab in...
the Switched group, although this difference was not statistically significant (pre-treatment baseline: 1.6±0.9 per year; at pre-benralizumab baseline: 0.5±0.3 per year, p=0.283; Fig. 3A). All patients except one were exacerbation-free at the point of switching between treatments; however, no difference was found in the clinically significant exacerbation rates (p=1.000; Fig. 3A). The annual clinically significant exacerbation rates in the Mepolizumab group decreased from 2.3±1.1 per year at the pre-treatment baseline to 0.2±0.2 per year after 1 year of treatment (p=0.156; Fig. 3B). However, the annual clinically significant exacerbation rates remained almost constant afterwards (0.3±0.2 per year after 2 years, p=0.947).

We found patients with reduced annual exacerbation rates requiring hospitalization during the treatment with mepolizumab in the Switched group, but without any statistical significance (pre-treatment baseline: 0.9±0.8 per year; pre-benralizumab baseline: 0.3±0.3 per year, p=0.859; Fig. 3C). None of the Switched group patients experienced hospitalization after 1 year of switching treatments (p=0.682; Fig. 3C). There was a trend toward a reduction in the annual exacerbation rates requiring hospitalization in the Mepolizumab group (pre-treatment baseline: 1.9±1.0 per year; after 1 year of treatment: 0.2±0.0 per year, p=0.072; Fig. 3D). The annual exacerbation rate requiring hospitalization remained reduced after that (p=0.880; Fig. 4A). A similar trend was observed in the Mepolizumab group, in which the FEV₁ value increased non-significantly from 1.14±0.04 L at pre-treatment baseline to 1.24±0.16 L after 1 year of treatment (p=0.841; Fig. 4B) and then slightly decreased to 1.13±0.19 L after 2 years of treatment (p=0.800; Fig. 4B).

The FEV₁/FVC ratio increased non-significantly in the Switched group from 47.1±6.0% to 49.5±6.9% during the mepolizumab treatment year (p=0.841; Fig. 4B) and then slightly decreased to 50.2±4.5 after 2 years of mepolizumab treatment (p=0.072; Fig. 4B). The FEV₁/FVC ratio increased non-significantly in the Mepolizumab group from 54.2±3.7 at the pre-treatment baseline to 56.3±3.5 after 1 year of mepolizumab treatment (p=0.892; Fig. 4C) and then slightly decreased to 50.2±4.5 after 2 years of mepolizumab treatment (p=0.072; Fig. 4D).

**Safety**

There were no significant adverse events such as headache, nasopharyngitis, arthralgia, or any injection site reactions during the study period.

**Discussion**

We investigated whether elderly patients with severe eosinophilic asthma could experience improved asthma control and lung function when switched directly from mepolizumab to benralizumab. We demonstrated in this study that switching treatment to benralizumab without a washout period reduced the blood eosinophil level to below the detection level. Other effects were observable but not statistically significant: the reduced annual exacerbation rate after switching treatments and eosinophil depletion benefited lung function slightly. Overall, there was no significant difference in the treatment response between the two groups. To the
best of our knowledge, this is the first study evaluating the effect of switching the treatment from mepolizumab to benralizumab in elderly patients with severe eosinophilic asthma.

Eosinophils are key inflammatory cell mediators in the pathogenesis of asthma (36). Blood and sputum eosinophilia were associated with poor disease control and a poor prognosis (37). Furthermore, blood eosinophilia was shown to often reflect asthma severity (38), and a relationship between the reduction in sputum eosinophils and the exacerbation rate was thus demonstrated (14, 39, 40). The effect of benralizumab on exacerbation reduction seems to be relatively strong. In our study, benralizumab reduced the blood eosinophils to below detectable levels, while mepolizumab did not yield such a robust reduction. The annual rate of clinically significant exacerbations and hospitalizations reduced after switching the therapy, although no statistically significant effect was observed. We speculate that the small number of subjects in this study may have resulted in a lack of statistical significance. Another reason for the lack of any significant difference could also be because five (83.3%) patients in the Switching group responded to the mepolizumab treatment. The clinically significant exacerbation rate in patients who continued with the mepolizumab treatment slightly decreased, but then remained almost constant. None of the patients required hospitalization due to exacerbations at 1 year after initiation of mepolizumab. Eosinophilic airway inflammation was reported to be one of the most influential traits in chronic airways disease (41). Therefore, controlling eosinophilic inflammation could be useful for treating severe asthma or preventing exacerbations. Our findings indicate that monoclonal antibodies directed against the IL-5 pathway are very effective therapeutic agents for patients with asthma in whom eosinophils play a dominant pathobi-
Figure 4. Treatment effect on lung function. The treatment effect on forced expiratory volume in one second (FEV1) during the study period in the Switched group (A) and the Mepolizumab group (B), FEV1/forced vital capacity (FVC) ratio measured over the study period in the Switched group (C) and in the Mepolizumab group (D).

We did not observe any notable change in FEV1 and the FEV1/FVC ratio in either group in this study. This could be due to the age-related airway remodeling and irreversible airway obstruction and COPD (42, 43). The mean age of the patients in this study was 76.3±1.5 years, which was considerably higher than that in previous clinical studies (the mean age of these subjects was 49.7 years) (21, 23-26). It has been proposed that airway remodeling might be the consequence of excessive repair processes following repeated airway injury (42). There is increasing evidence that eosinophils might be important in the pathophysiology of remodeling (44). Future long-term investigation is therefore required to determine whether anti-IL-5 monoclonal antibodies can prevent the progression of airway remodeling.

In the present study, almost all patients responded to mepolizumab, and the primary reason for switching to benralizumab was the reduced frequency of regular treatment. However, some patients wished to continue mepolizumab treatment because of the adequate treatment response and short duration of hospital visits. Drick et al. reported that switching to benralizumab led to significantly improved asthma control (28). Although we did not record the asthma control status and symptoms in all patients, we speculate that some patients might have had persistent asthma symptoms despite mepolizumab treatment, and that benralizumab may have ameliorated the asthma symptoms in some patients.

Although elderly patients were included in this study, no adverse events were recorded, thus suggesting that their occurrence rate due to mepolizumab and benralizumab was low, as observed in several previous clinical studies (25, 26, 31, 45, 46). While anti-benralizumab, anti-mepolizumab, or
neutralizing antibodies were not evaluated in this study, eosinophil depletion was maintained over the study period. Along with these results, the immunogenicity profile of benralizumab was similar to that reported in several previous clinical studies (46, 47).

The main limitation associated with this study is the small number of patients that could have altered the results of statistical analyses; however, the number of patients in this age range is quite small, so we could not recruit more patients. Moreover, there were no statistically significant differences in the baseline clinical characteristics between the Switched and Mepolizumab groups; this could also be attributed to the small sample size. In addition, the patient background was not balanced between the two groups, and this may also have influenced the results.

There were some additional important limitations associated with this analysis. First, there was great variability among the patients in the sample, and their different treatments were not considered during the analysis. Second, this was a retrospective study. Third, although the exacerbation rates appeared to decrease, their estimation was prone to error because of the short follow-up period. Finally, there was no washout period after mepolizumab treatment. The first dose of benralizumab was administered when mepolizumab had not been fully eliminated from the body. Thus, a large prospective study involving a larger numbers of patients is required to evaluate the efficacy and safety of switching from mepolizumab to benralizumab treatment in patients with severe eosinophilic asthma not optimally controlled by mepolizumab.

Conclusion

Switching from mepolizumab to benralizumab without a washout period was found to reduce the absolute blood eosinophil counts. Although this study was based on a small sample size, there was no clear difference in the treatment response between mepolizumab treatment and treatment involving a direct switch from mepolizumab to benralizumab. These findings indicate that both treatments may have clinically relevant asthma control benefits for elderly patients with severe eosinophilic asthma. Future prospective, multicenter clinical trials with larger sample sizes are necessary to verify these results.

Author’s disclosure of potential Conflicts of Interest (COI).

Nobuhisa Ishikawa: Honoraria, AstraZeneca and GlaxoS- SmithKline. Noboru Hattori: Honoraria, AstraZeneca and GlaxoS- SmithKline.

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