Effectiveness and safety of benralizumab for severe asthma in clinical practice (J-BEST): a prospective study

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Background: Benralizumab is a humanized, fucosylated, monoclonal antibody that targets the interleukin 5 (IL-5) α receptor. Several phase III trials have shown that benralizumab can significantly reduce the incidence of acute exacerbations and improve lung function in patients with severe asthma. However, there is a paucity of data from clinical practice. In this prospective study, we evaluated the effectiveness and safety of benralizumab for severe asthma in clinical practice.

Methods: This was a prospective, open-label, single-arm, single-center study in patients with severe asthma in clinical practice (UMIN000031951). Haematological, clinical, functional, and pharmacotherapeutic parameters were evaluated at baseline and at weeks 4 and 12 after initiation of benralizumab.

Results: Twenty-six patients were enrolled between May 2018 and March 2019. Both asthma quality of life questionnaire (AQLQ) score and asthma control test (ACT) score showed significant improvement over the study period. Forced expiratory volume in 1.0 second (FEV1) showed a significant increase at week 12 (baseline: 1.57 L; week 12: 1.75 L). Blood eosinophil and basophil counts were significantly decreased at week 12 compared to baseline. At week 12, the dose of regular oral corticosteroids (OCS) was significantly decreased from baseline as was the number of patients on need-based OCS. Benralizumab had no significant effect on fractional exhaled nitric oxide (FeNO) levels and total immunoglobulin E levels. Only one patient experienced mild headache during benralizumab therapy.

Conclusions: In this study, benralizumab conferred clinically significant benefits in patients with severe asthma with no short-term severe adverse events.

Keywords: Basophils; eosinophils; interleukin-5 receptor α monoclonal antibody; oral corticosteroids (OCS)

Submitted Dec 11, 2019. Accepted for publication Mar 12, 2020.
doi: 10.21037/atm.2020.04.01
View this article at: http://dx.doi.org/10.21037/atm.2020.04.01

Introduction

Bronchial asthma is one of the most common respiratory diseases, which affects individuals in all age-groups (1). The last twenty years have witnessed a considerable decrease in the number of emergency outpatient visits and hospitalizations due to acute exacerbations of bronchial asthma; in addition, there has been a steady decrease in deaths due to bronchial asthma since the mid 1990s (2). This phenomenon is mainly due to improved asthma control achieved by maintenance treatment with inhaled corticosteroids (ICS), either alone or in combination with a second controller, generally a long-acting beta2 agonist (LABA), depending on asthma severity (3). However, bronchial asthma is a heterogenous disease with considerable inter-individual variability with respect to the
clinical course (4-6).

ICS therapy is the mainstay of treatment of bronchial asthma, which is supplemented with LABAs, long-acting muscarinic antagonists (LAMA), and leukotriene receptor antagonist (LTRA), as appropriate. Nonetheless, some patients do not adequately respond to these treatments (7). Anti immunoglobulin E (IgE) antibody, anti interleukin 5 (IL-5) antibody, anti IL-5 receptor alpha antibodies, and IL-4/13 receptor antibodies have been approved for maintenance treatment of severe asthma patients with eosinophilic phenotype who are not adequately controlled by standard of care (8). These new drugs may be effective in cases where conventional treatment fails to prevent asthma exacerbations.

Benralizumab is a humanized, fucosylated, monoclonal antibody that targets the IL-5 α receptor (9). In contrast to anti–IL-5 monoclonal antibodies including mepolizumab and reslizumab, benralizumab induces direct, rapid, and nearly complete depletion of blood eosinophils through enhanced antibody-dependent cell-mediated cytotoxicity (ADCC), an apoptotic process of eosinophil elimination involving natural killer cells (10). In two Phase III trials (SIROCCO and CALIMA), benralizumab administered in combination with high-dose ICS/LABA significantly reduced acute exacerbations of asthma and improved lung function and disease control in patients with severe uncontrolled asthma and blood eosinophil counts ≥300/μL as compared to placebo (11,12). In another Phase III trial (ZONDA), benralizumab significantly reduced the use of maintenance prednisone in oral corticosteroid (OCS)-dependent patients while maintaining asthma control (13). Statistical analyses of these phase III studies identified several baseline clinical factors associated with enhanced efficacy of benralizumab, regardless of blood eosinophil counts; these included OCS use, history of nasal polyposis, lung function (as assessed by prebronchodilator forced vital capacity), exacerbation frequency, and age at asthma diagnosis (13).

However, there are no prospective studies in clinical practice. Therefore, we performed a prospective study to assess the effects of benralizumab in patients with severe asthma.

Methods

J-BEST was a prospective, open-label, single-arm, single-center study in patients with severe asthma in clinical practice. This study was approved by the ethics committee at the Japanese Red Cross Medical Center (No.869) and registered at the University Hospital Medical Information Network (UMIN, 00003195). Written informed consent was obtained from all patients prior to their enrolment. Patients with uncontrolled severe asthma who were aged ≥20 years were eligible for inclusion. These patients had persistent symptoms despite regular treatment with high-dose inhaled ICS/LABA, and had also received LAMA and LTRA with or without OCS therapy and biological agents other than benralizumab at the step 5 for Global Initiative for Asthma (GINA) or at the step 4 for Japanese guidelines for bronchial asthma. This study was conducted from May 2018 to Mar 2019. Overall, 26 patients were enrolled.

Patients were prescribed a single subcutaneous injection of benralizumab (30 mg) administered at intervals of 4 weeks for the first three injections, and every 8 weeks thereafter. Haematological, clinical, functional, and pharmacotherapeutic parameters were recorded at baseline and at weeks 4 and 12 after initiation of benralizumab therapy. Hematological parameters included total eosinophil count, total basophil count, and serum IgE level. Other parameters recorded were asthma quality of life questionnaire (AQLQ) score, asthma control test (ACT) score, prebronchodilator FEV1 (only at baseline and at week 12), peak expiratory flow (PEF, only at baseline and at week 12), fractional exhaled nitric oxide (FeNO), oral prednisone dose, and adverse events (AEs). The primary endpoint was mean change in AQLQ and ACT scores from baseline at week 12. Additional endpoint was mean change in FEV1 from baseline at week 12. The safety endpoint was the frequency of AEs, which included any adverse medical event (including abnormal laboratory changes) that occurred after treatment, with or without a causal relationship with the treatment. AEs were recorded on a worksheet by patients and documented by physicians.

A sample size of 25 was calculated using an expected value of 0.75 and a threshold of 0.50 with a two-tailed statistical significance of α=0.05 and a power of at least 0.80. Allowing for missing data (due to patient dropout), we planned to recruit 26 patients to the present study. Descriptive statistics are presented as mean (95% confidence interval, CI) or as frequency (percentage). The Fischer exact test for categorical data and Mann-Whitney U test for numeric data were used to evaluate the significance of difference in the native and switched groups. Kruskal-Wallis test for paired data was used to evaluate the significance of difference in baseline, week 4 and week 12 of the time course of the treatment. All reported P values were two-sided, and P values <0.05 were considered statistically significant.
Table 1 Baseline demographic and clinical characteristics of the study population

| Characteristics                                      | All patients, (n=26) | Naive group (n=16) | Switched group, (n=10) | P value |
|------------------------------------------------------|----------------------|--------------------|------------------------|---------|
| Age (years)                                          | 66.8 [60.9–72.8]     | 65.8 [56.6–75.2]   | 68.4 [61.7–75.0]       | 0.679   |
| Female sex [n (%)]                                   | 15 [57.7]            | 8 [50.0]           | 7 [70.0]               | 0.473   |
| BMI (kg/m²)                                          | 25.1 [22.9–27.8]     | 26.1 [22.8–29.4]   | 23.4 [21.4–25.5]       | 0.215   |
| Prebronchodilator FEV1 (liters)                      | 1.57 [1.31–1.84]     | 1.74 [1.36–2.11]   | 1.3 [0.95–1.67]        | 0.111   |
| Peak flow (liters/min)                               | 314 [255–373]        | 355 [270–440]      | 248 [176–321]          | 0.071   |
| No. of exacerbations in the past year                | 3.7 [2.4–4.9]        | 4.4 [1.5–7.3]      | 3.5 [1.2–5.7]          | 0.773   |
| Use of regular oral glucocorticoids (mg/day)         | 4.1 [1.6–6.5]        | 4.4 [1.6–7.3]      | 3.5 [1.5–8.5]          | 0.706   |
| Use of regular oral glucocorticoids [n (%)]          | 10 [38.5]            | 7 [43.8]           | 3 [30.0]               | 0.683   |
| Use of as-needed basis oral glucocorticoid [n (%)]   | 19 [73.1]            | 13 [81.2]          | 6 [60.0]               | 0.369   |
| ACT score                                            | 14 [11–17]           | 14 [10–17]         | 14 [9.3–19]            | 0.954   |
| AQLQ score                                           | 4.2 [3.6–4.8]        | 4.3 [3.4–5.1]      | 4.1 [3.2–4.9]          | 0.688   |
| Eosinophilic polyposis or rhinosinusitis [n (%)]     | 6 [23.1]             | 2 [6.3]            | 4 [40.0]               | 0.163   |
| Former smoker [n (%)]                                | 8 [30.8]             | 5 [31.3]           | 3 [30.0]               | 1.00    |
| Biomarker levels                                    |                      |                    |                        |         |
| Blood eosinophil count (cells/mm³)                   | 241 [99–380]         | 353 [137–568]      | 59 [12–105]            | 0.033   |
| Blood basophil count (cells/mm³)                     | 34 [24–44]           | 38 [23–54]         | 28 [16–39]             | 0.299   |
| FeNO (ppb)                                           | 53 [35–71]           | 56 [30–81]         | 50 [20–79]             | 0.730   |
| Total IgE (IU/mL)                                    | 495 [145–846]        | 294 [36–552]       | 817 [62–1,697]         | 0.138   |
| Perennial allergen positive                           | 12 [46.2]            | 7 [43.8]           | 5 [50.0]               | 0.785   |

Data presented as mean [95% confidence interval] or n [%]. P values refer to the comparison between naive group and switched group. BMI, body mass index; FEV1, forced expiratory volume in 1.0 second; FeNO, fractional exhaled nitric oxide; ACT, asthma control test; AQLQ, asthma quality of life questionnaire.

indicative of statistical significance. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) (14).

Results

Baseline demographic and clinical characteristics of patients are summarized in Table 1. The mean age of patients was 66.8 years; 15 patients were women. Ten out of the 26 patients had previously received biological drugs (omalizumab: 2 patients; mepolizumab: 8 patients). The mean prior omalizumab and mepolizumab treatment duration were 12.5 months and 9.0 months, respectively.

The time course of benralizumab treatment is described in Table 2. The AQLQ scores of patients showed a significant improvement over the study period [baseline: 4.2 (mean, 95% CI) (3.6–4.8); week 4: 5.4 (5.0–5.8) (P<0.001 vs. baseline); week 12: 5.6 (5.1–6.1) (P<0.0001 vs. baseline)]. The ACT scores also showed a significant improvement over the study period [baseline: 14 [11–17]; week 4: 19 [17–21] (P<0.001 vs. baseline); week 12: 20 [19–22] (P<0.001 vs. baseline)]. This improvement was maintained over the study period in 20 patients (77%) at week 12. FEV1 increased from 1.57 L (1.31–1.84) at baseline to 1.75 L (1.46–2.03) at week 12 (P=0.003). Peak flow increased from 314 L/min [255–373] at baseline to 369 L/min [307–431] at week 12 (P<0.001). Pulmonary function (FEV1) of 19 out of 26 patients (73.1%) improved over the study period at week 12. The dose of regular OCS decreased from 4.1 (1.6–6.5) mg at baseline to 1.2 (0–2.5) mg at week 12.
Table 2 Time course of benralizumab treatment

| Characteristics                                      | Baseline       | Week 4         | Week 12        | P value |
|------------------------------------------------------|----------------|----------------|----------------|---------|
| Prebronchodilator FEV1 [liters]                      | 1.57 [1.31–1.84] | 1.75 [1.46–2.03] | <0.001         |         |
| Peak flow [liters/min]                               | 314 [255–373]  | 369 [307–431]  | <0.001         |         |
| Use of regular oral glucocorticoids [mg/day]         | 4.1 [1.6–6.5]   | 1.2 [0–2.5]    | 0.008          |         |
| Use of regular oral glucocorticoids [n (%)]          | 10 [38.5]       | 4 [15.4]       | 0.116          |         |
| Use of need-based oral glucocorticoids [n (%)]       | 19 [73.1]       | 2 [7.7]        | <0.0001        |         |
| ACT score                                            | 14 [11–17]      | 19 [17–21]     | <0.0001        |         |
| AQLQ score                                           | 4.2 [3.6–4.8]   | 5.4 [5.0–5.8]  | <0.0001        |         |

Biomarker levels

| Biomarker levels                                      | Baseline       | Week 4         | Week 12        | P value |
|------------------------------------------------------|----------------|----------------|----------------|---------|
| Blood eosinophil count [cells/mm³]                   | 241 [99–380]   | 0 [0–0]        | <0.0001        |         |
| Blood basophil count [cells/mm³]                     | 34 [24–44]     | 7 [4–11]       | <0.0001        |         |
| FeNO [ppb]                                           | 53 [35–71]     | 59 [36–82]     | 0.90           |         |
| Total IgE [IU/mL]                                    | 495 [145–846]  | 438 [139–736]  | 487 [160–813]  | 1.00    |

Data presented as mean [95% confidence interval] or n [%]. P values refer to comparison between baseline level and week 12. FEV1, forced expiratory volume in 1.0 second; FeNO, fractional exhaled nitric oxide; ACT, asthma control test; AQLQ, asthma quality of life questionnaire.

In this study, 8 patients changed from mepolizumab to benralizumab. In these 8 patients, the total eosinophil count in blood showed a significant decrease over the study period: baseline: 241 [99–380] cells/mm³; week 4: 0 [0–0] (P=0.005 vs. baseline); week 12: 0 [0–0] (P=0.005 vs. baseline). Similarly, blood basophil count also showed a significant decrease over the study period: baseline: 241 [99–380] cells/mm³; week 4: 0 [0–0] (P=0.005 vs. baseline); week 12: 9 [7–11] (P<0.001 vs. baseline). However, there were no significant changes in the level of FeNO (baseline: 53 ppb [35–71]; week 4: 59 ppb [36–82]; week 12: 61 ppb [37–86], P=0.9). Similarly, there was no significant change in total IgE level (baseline: 495 [145–846] IU/mL; week 4: 438 [139–736] (P=0.45 vs. baseline); week 12: 487 [160–813] (P=1.0 vs. baseline).

In this study, 8 patients changed from mepolizumab to benralizumab. In these 8 patients, the total eosinophil count in blood showed a significant decrease over the study period: baseline: 32 [14–51] cells/mm³; week 4: 0 [0–0] (P=0.012 vs. baseline); week 12: 0 [0–0] (P=0.012 vs. baseline). Moreover, blood basophil count also showed a significant decrease at week 12: baseline: 30 [18–42] cells/mm³; week 4: 21 [2–21] (P=0.091 vs. baseline); week 12: 10 [3–16] (P=0.046 vs. baseline).

Only one patient experienced slight headache that did not require any pharmacologic treatment.

Discussion

To the best of our knowledge, this is the first prospective study of the effect of benralizumab in patients with severe asthma in clinical practice. In this study, benralizumab was found to be highly effective against severe asthma at weeks 4 and 12 after administration.

Patients with severe asthma account for an estimated 5–10% of all asthma patients. The estimated cost of treatment of these patients accounts for as much as 50% of all costs of asthma treatment (15). Patients with severe asthma have been stratified based on phenotype and endotype; this has facilitated a better understanding of the pathophysiology of airway inflammation and enabled development of novel therapies for severe asthma (16).

The Th2 cytokines (IL-4, IL-5, IL-9, and IL-13) play an important role in the pathogenesis and acute exacerbations of bronchial asthma (17). In recent years, anti-IgE antibodies were the first to be approved for treatment of severe asthma; subsequently, anti-IL-5 antibodies, anti-IL-5 receptor α antibodies, and IL-4/13 receptor antibodies were also approved for clinical use. Studies have demonstrated the effectiveness of biological products (16,18). These developments have heralded the era of
precision medicine for severe asthma. Eosinophilic asthma, which is characterized by eosinophilic airway inflammation, accounts for approximately half of all patients with severe asthma (19). Asthmatic patients with high eosinophil counts have a strong predisposition to allergy, impaired respiratory function, and a high frequency of exacerbations (20).

In our study, benralizumab was effective as early as 4 and 12 weeks after administration. A significant improvement in subjective scores (ACT and AQLQ scores) was observed 4 weeks after administration of benralizumab; the effect was sustained even 12 weeks after administration of benralizumab. Prompt improvement in symptoms is a key imperative in patients with severe asthma; benralizumab administration was found to be very useful for patients with severe asthma in this study. Furthermore, FEV1 and peak flow after 12 weeks of benralizumab was significantly improved compared with pre-treatment levels. In addition, a significant decrease in the dose of OCS was observed 12 weeks after administration of benralizumab. It is well known that continuous administration of OCS may cause various complications, and it is very important to reduce the use of OCS for asthma in clinical practice (21).

In this study, the mean total eosinophil count in the blood at 4 weeks after benralizumab therapy was 0 cells/mm³. We had earlier reported a significant decrease in eosinophils in lung and bronchial tissues in surgically resected specimens after administration of benralizumab (22). We believe that the improvement in FEV1 and peak flow was attributable to the decrease in the number of tissue eosinophils consequent to the nil eosinophil count in the blood. In this study, the basophil count was also significantly decreased at week 4 and 12 after administration of benralizumab. Basophils are known to exhibit surface expression of anti-IL-5 receptor. In a study, treatment with mepolizumab (an anti-IL-5 antibody) did not lead to a decrease in basophils; the decrease in blood basophils in the present study may reflect the difference between anti-IL-5 antibodies and anti-IL-5 receptor antibodies (7,23). In our study, 8 patients changed from mepolizumab to benralizumab. In these 8 patients, the both total eosinophil count and basophil count in blood showed a significant decrease in this study. This might be the reason why patients who switched from mepolizumab to benralizumab were also effective.

In our study, benralizumab did not reduce the levels of FeNO or total IgE level. These results are consistent with the results of previous clinical trials of benralizumab (11,12). The therapeutic effects of benralizumab might not depend on the levels of FeNO or total IgE level.

This study had several limitations. Although this study was a prospective study, it was conducted at a single health facility. Prospective multicenter studies may provide more definitive evidence. Second, there was the lack of a control group of severe asthma patients who were on standard of care in this study. In clinical practice, it was very difficult to set a control group without biological products because of patient’s care. Third, our study included both patients who were switched from other biological products to benralizumab and those who received a biological product for the first time. The study was conducted without preparing a special environment as much as possible for examination in clinical practice. In addition, we could not assess the patients who are more likely to benefit from switching to benralizumab. However this is considered to be an important point of view in clinical practice, the number of cases calculated in this study was not enough to compare in each group. Further investigations are needed to clarify this aspect.

Conclusions
Benralizumab conferred clinically significant benefits in patients with severe asthma with no associated serious AEs in the short term in clinical practice. More studies are required to provide more robust evidence of the benefits of benralizumab in particular as compared with other biologics approved for severe asthma in clinical practice. Future studies should identify treatable traits, as a step towards precision medicine for severe asthma.

Acknowledgments
Funding: None.

Footnote
Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi. org/10.21037/atm.2020.04.01). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the ethics committee at the Japanese Red Cross Medical Center (No. 869) and registered at the University Hospital Medical Information Network (UMIN, 00003195).
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Cite this article as: Izumo T, Tone M, Kuse N, Awano N, Tanaka A, Jo T, Yoshimura H, Minami J, Takada K, Inomata M. Effectiveness and safety of benralizumab for severe asthma in clinical practice (J-BEST): a prospective study. Ann Transl Med 2020;8(7):438. doi: 10.21037/atm.2020.04.01