STUDY REPORT SYNOPSIS

HAYATE study

Comparative study of the efficacy of biologics vs usual treatment on OCS reduction for severe asthma patients using health insurance claim database

Milestones:	Clinical Study Report Approved
Phase of development:	Post-Marketing
Sponsor:	AstraZeneca
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This study was conducted in accordance with the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects.

Background/rationale: Asthma is a chronic inflammatory disease of the airways characterized by airway constriction and airway hyper-responsiveness with wheezing, cough and exacerbations. About 5-10% of asthmatic patients experience the most severe disease, thus requiring further therapy such as oral corticosteroids (OCS) etc, despite high amount of inhaled corticosteroids (ICS)/long-acting beta2 agonist (LABA) treatment. Some patients with severe asthma also experience recurrent exacerbations and characteristically show eosinophilic inflammation. Patients with severe asthma receiving maintenance treatment with OCS may experience increased risk of chronic comorbidities. Therefore, reduction of OCS exposure is an important treatment goal for patients with severe asthma.

As of January 2021, four monoclonal antibodies (biologics [BIO], these are benralizumab, omalizumab, dupilumab and mepolizumab) were available in clinical practice in Japan. BIO treatment showed efficacy for exacerbation reduction in Phase 3 studies. In addition to reduction of exacerbation, the possibility of OCS-sparing has been demonstrated by each BIO treatment. Although evidence from Phase 3 studies are important, Phase 3 study is different from a real-world setting. Management of OCS reduction including OCS reduction speed is determined by physicians on the basis of patient's symptoms, amount of OCS use etc in a real-world setting, while OCS reduction criteria is defined by a protocol in Phase 3 studies. Each BIO showed efficacy for exacerbation, quality of life, etc in real-world evidence (RWE). However, there is not enough RWE on the impact of BIO treatment on OCS reduction, particularly in Japan. In health insurance claims database (Medical Data Vision [MDV] database), there is now sufficient data of severe asthma patients treated with BIO. Therefore, the aim of this study was to use this database to evaluate effectiveness of BIO on OCS reduction for OCS-dependent severe asthma patients compared to BIO non-initiated patients.

Objectives: The aim of the study was first to investigate OCS reduction between the BIO initiated severe asthma patients with regular maintenance OCS and the BIO non-initiated severe asthma patients with regular maintenance OCS use, and second to assess the rate of achievement of the daily dose reduction rates for maintenance OCS between the BIO initiated severe asthma patients with regular maintenance OCS use and the BIO non-initiated severe asthma patients with regular maintenance OCS use as well as between each BIO treatment. Moreover, this study would investigate cumulative doses of maintenance ICS and systemic corticosteroids (SCS), the incidence rate of the asthma-related exacerbation, and the change of the concomitant medications associated with each BIO treatment.

Study design: This study was a retrospective cohort study of patients diagnosed with asthma on the basis of the data extracted from the MDV database. The study period was from 22nd

December 2015 to 29th February 2020. The baseline period was set as 24 weeks prior to the index date, and the outcome period was set as 24 weeks after the index date.

<Definition of the index date>

- For the BIO initiated group: the date when the BIO treatment was prescribed for the first time after 7th June 2016.
- For the BIO non-initiated group: the date when maintenance OCS (See Section 4.3.1) was prescribed after 7th June 2016 and met inclusion criterion #4 (See Section 3.3). If multiple dates were identified for a patient, the index date was to be selected randomly from those candidates.

Data source: MDV database
Study population: Patients diagnosed with asthma (International Classification of Diseases [ICD] -10 code: J45 or J46) and received high-dose ICS or high-dose ICS/LABA prescription at least once within 24 weeks prior to the index date.
Inclusion criteria:
Patients aged ≥16 years at the index date.
Patients with records of receiving high-dose ICS or high-dose ICS/LABA and diagnosed as asthma (ICD-10 code: J45 or J46) during the baseline period.
Patients who had visit histories at least one visit during the baseline period, at least two visits during the outcome period and at least one visit after the outcome period.
Patients who had a total of 12 weeks of OCS prescribed during the baseline period including the index date.
Exclusion criteria:
Patients diagnosed with selected autoimmune diseases during the baseline period because OCS was used as a therapeutic agent for these diseases. Autoimmune diseases were identified by the following ICD-10 code (M30, M05, M06, L93, M32, K50, K51, K52, and N04).
Statistical methods: All data were summarized using appropriate descriptive statistics by group. For categorical variables, the number of patients and the percentage were calculated. For quantitative variables, the number of patients, mean, standard deviation (SD), median, maximum, minimum and quartiles were calculated.
The primary endpoint, proportion reduction on daily maintenance OCS dose from week-0 to week-24, was to be tested at 2-sided significance level 0.05.
Inverse probability of treatment weighting (IPTW) method was applied to balance baseline covariates between the treatment groups.
Statistical analysis included two Phases, Phase 1 and Phase 2. In Phase 1, descriptive analysis was conducted about baseline data and the validity to apply the IPTW methods was evaluated. If the IPTW methods were considered to be suitable, then the comparison between the BIO treated group and the non-BIO initiated group was to be made using IPTW in Phase 2 as follows:
The proportion reduction on daily maintenance OCS dose from week-0 to week-24, the primary outcome, was to be compared between the BIO and BIO non-initiated groups using functional response model-based causal Wilcoxon rank-sum test[21] approach with IPTW weights. The proportion reduction on daily maintenance OCS dose from week-0 to week-8 and week-16 were to be similarly tested.
The proportion of patients who achieved maintenance OCS reduction, was to be analyzed on the basis of the logistic regression model including treatment groups as a covariate using IPTW weights. Odds ratio (OR) between the treatment groups, its 95% confidence interval (CI) and p-value were to be presented on the basis of the logistic regression model.
Results: Overall, 3,081,923 patients with a diagnosis of asthma were identified between 22nd December 2015 and 29th February 2020 in the MDV database. Of these, 2,927 patients were eligible for the study and included in the study population. Of the 2,927 patients, 239 patients were included in the BIO initiated group and 2,688 patients in the BIO non-initiated group.
For all patients included in the Full Analysis Set (FAS), the mean (SD) age was 67.5 (14.37) years, and 52.7% (1,542 patients) were female. For the BIO initiated group and

the BIO non-initiated group, the mean (SD) age was 63.9 (14.04) years and 67.8 (14.36) years, respectively. 61.1% (146 patients) were female in the BIO initiated group and 51.9% (1,396 patients) were female in the BIO non-initiated group.

In the Phase 1 in the statistical analysis, no pairs of covariates had Spearman's correlation greater than 0.7 in the continuous version of the logistic model, which indicated that no covariates were highly correlated. No extreme values were found; thus, we assumed that the positivity was satisfied and that there was no clear misspecification of the propensity score model. Neither the categorical version of model nor the continuous version of model could meet the prespecified condition that mean standardized differences in the weighted sample should be less than or equal to 0.10 for all covariates. The number of covariates with the difference greater than 0.10 was smaller in the continuous version compared to the categorical version; thus, we decided to perform Phase 2 analysis using the continuous version of model without statistical tests.

In IPTW-adjusted analysis, the median proportion reduction of the daily dose of maintenance OCS was 25.0% (interquartile range [IQR]: 0.0% to 100%) in the BIO initiated group and 0.0% (IQR: 0.0% to 83.3%) in the BIO non-initiated group at week-24. The mean (SD) proportion reduction of the daily dose of maintenance OCS was 22.7 (120.64)% in the BIO initiated group and 20.3 (92.85)% in the BIO non-initiated group. The median difference of proportion reduction between the groups was 0.0000% (Hodges-Lehmann estimate, 95% CI: 0.0000, 0.3365).

The proportion of patients who achieved >0%, ≥25%, ≥50%, or 100% reduction of the daily maintenance OCS dose at week-24 was numerically higher in the BIO initiated group than in the BIO non-initiated group. The proportion of patients who achieved >0% reduction of the daily maintenance OCS dose was 56.6% in the BIO initiated group versus (vs) 44.1% in the BIO non-initiated group (OR, 1.6554 [95% CI: 1.4907, 1.8384]); those who achieved ≥25% reduction was 50.5% vs 40.6% (OR, 1.4888 [95% CI: 1.3405, 1.6535]); those who achieved ≥50% reduction was 42.8% vs 33.7% (OR, 1.4714 [95% CI: 1.3214, 1.6384]); and those who achieved 100% reduction was 26.2% vs 24.4% (OR, 1.1005 [95% CI: 0.9764, 1.2404]).

The median total amount of maintenance OCS (prednisolone equivalent) prescribed during the outcome period was 661.5 mg (IQR: 352.0 to 1,060.0 mg) in the BIO initiated group and 696.0 mg (IQR: 338.0 to 966.3 mg) in the BIO non-initiated group. The median total amount of SCS (prednisolone equivalent cumulative SCS doses) prescribed during the outcome period was 797.0 mg (IQR: 420.0 to 1,345.0 mg) in the BIO initiated group and 840.0 mg (IQR: 420.0 to 1,263.5 mg) in the BIO non-initiated group.

At week-8, the median proportion reduction of the daily dose of maintenance OCS was 0.0% in both groups, and the mean proportion reduction was 9.7% in the BIO initiated group and 17.2% in the BIO non-initiated group, with the median difference in the proportion reduction between the groups being 0.0000% (Hodges-Lehmann estimate, 95% CI: 0.0000, 0.0000). At week-16, the proportion reduction of the daily dose of maintenance OCS was numerically higher in the BIO initiated group than in the BIO non-initiated group. The median proportion reduction of the daily dose of maintenance OCS was 22.2% in the BIO initiated group and 0.0% in the BIO non-initiated group at week-16, and the mean corresponding proportion reduction was 26.7% and 17.1% respectively, with the median difference in the proportion reduction between the groups being 0.0225% (95% CI: 0.0000, 1.1845).

In unadjusted analysis, the median proportion reduction of the daily dose of maintenance OCS was 33.3% in the benralizumab or mepolizumab initiated group and 0.0% in the BIO non-initiated group, and the mean corresponding proportion reduction was 31.0% and 20.4% respectively. The median difference in the proportion reduction between the groups was 0.0000% (Hodges-Lehmann estimate, 95% CI: 0.0000, 0.0000).
The unadjusted median total amount of maintenance OCS (prednisolone equivalent) prescribed for one year and two years was numerically greater in the BIO initiated group with 1,475.3 mg than in the BIO non-initiated group with 1,147.5 mg for one year, and 3,010.0 mg and 1,655.0 mg for two years respectively. The unadjusted median total amount of maintenance SCS (prednisolone equivalent cumulative SCS doses) prescribed for one year and two years was also numerically greater in the BIO initiated group with 1,871.5 mg than in the BIO non-initiated group with 1,513.8 mg for one year, and 3,887.5 mg and 2,165.0 mg for two years respectively.
Conclusion: This retrospective database study found that the daily dose of maintenance OCS was reduced with BIO treatment among severe asthma patients. In IPTW-adjusted analysis, the proportion of patients who achieved >0%, ≥25%, ≥50%, or 100% reduction of the daily maintenance OCS dose at week-24 was numerically higher in the BIO initiated group than in the BIO non-initiated group. However, no clear difference was observed in OCS reduction between the patients with BIO treament and those with no BIO treatment in this study (median difference of proportion reduction was 0.0000%, 95% CI: 0.0000, 0.3365). Since this result may have been affected by several limitations in this study, further research with a longer observation period and variables that could not be considered in the current study is required.
Publications: Presentation at Congress: The 71st Annual Meeting of The Japanese Society of Allergology, October 2022. Publication: To be determined.