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CETB115GKR02 Study Results Abstract for Public Disclosure

Title

Retrospective Chart Review of Safety and Effectiveness of Eltrombopag in Combination With Immunosuppressive Therapy (IST) in Korean Pediatric Patients with Treatment Naïve Severe Aplastic Anemia

Keywords

Eltrombopag, retrospective chart review, safety

Rationale and background

Severe aplastic anemia (sAA) is a life-threatening, rare, acquired bone marrow failure disorder characterized by trilineage bone marrow hypoplasia and a deficiency of hematopoietic stem and progenitor cells due to immune-mediated attack on the bone marrow.

For young patients with a suitable and available donor, first-line treatment of choice is allogeneic hematopoietic stem cell transplantation (HSCT), which is curative and thus preferred when feasible.

One of the most promising recent treatments for aplastic anemia (AA) is eltrombopag, an oral thrombopoietin (TPO) receptor agonist previously approved for the treatment of chronic immune thrombocytopenia (ITP). Eltrombopag has been reported to improve hematologic responses in patients with refractory AA and when added to prior IST, showing multilineage effects. Eltrombopag interacts with the transmembrane domain of the TPO receptor (TPO-R) on megakaryocytes and human bone marrow progenitor cells, promoting hematopoiesis by stimulating proliferation and differentiation of early bone marrow progenitors. The multilineage effects of eltrombopag in patients with AA may be due to stimulation of bone marrow progenitor cells, as suggested by recent preclinical studies.

The efficacy and safety of eltrombopag in treatment-naïve patients with sAA were demonstrated in a global clinical trial—a non-randomized, single-center, open-label Phase I/II study (NCT01623167). This study investigated the combination of eltrombopag with standard IST, consisting of horse-antithymocyte globulin (h-ATG) and cyclosporine A (CsA), in patients aged 2 years or older with sAA who had not previously received definitive IST. The treatment regimen initiating eltrombopag concurrently with IST showed the highest rate of improvement in hematologic parameters, with robust and consistent early hematologic recovery observed without any new or unexpected safety signals. Furthermore, long-term survival of responders was associated with strong early hematologic recovery. However, the efficacy of adding eltrombopag to IST in pediatric patients with sAA remains unclear due to limitations in previous clinical trials, including small sample sizes, heterogeneity in eltrombopag dosing and timing, and lack of control groups.

In Korea, the incidence of pediatric sAA is approximately 5.16 cases per million population per year, resulting in a small patient population. Therefore, data on the addition of eltrombopag to first-line IST in Korean pediatric patients with sAA remain limited. As part of the risk management plan (RMP) for eltrombopag, Novartis Korea committed to conducting a proactive surveillance program in agreement with health authorities (HA). Accordingly, this study is designed to evaluate the safety and efficacy of eltrombopag when added to IST in treatment-naïve Korean pediatric patients with sAA following its approval for this indication.

Research question and objectives

To investigate the safety, tolerability and effectiveness of eltrombopag in combination with IST in real world practice in pediatric population in Korea.

Study design

This study adopted a retrospective, single-cohort design using data over a 6-month period extracted from patients' medical charts (electronic medical records) starting from the initiation of eltrombopag treatment.

This retrospective, non-interventional, multicenter, observational chart review study collected longitudinal medical record data of patients in real-world clinical practice.

Setting and study population

At each clinical site, all pediatric patients with sAA who met all of the following eligibility criteria were included in the study.

Eligibility Criteria

To be eligible for inclusion in the study, patients were required to meet all of the following criteria:

1. Male or female pediatric patients aged ≥2 years and <18 years at the time of initiation of eltrombopag and IST treatment.
2. Subjects diagnosed with sAA and treated with eltrombopag in combination with IST as first-line therapy, based on the physician's decision in accordance with locally approved prescribing information at the time of data collection.
3. Subjects for whom the analytical index date (defined as the start date of eltrombopag treatment) was at least 6 months prior to the data extraction date.

Study size including dropout rate

As this study was part of the RMP requested by the Korean HA, every effort was made to collect the maximum amount of patient data in order to meet HA requirements. Efforts were undertaken to engage as many clinical sites as possible, capable of treating pediatric patients with sAA, and an estimate of the number of patients expected to be enrolled during the study period was made for planning purposes. From March 2023 (three years after the approval of the relevant indication for eltrombopag in Korea on March 18, 2020) to the end of data collection in March 2025, a total of 13 pediatric patients with sAA were enrolled in this study. Among them, 2 patients were excluded from the final analysis population due to violation of eligibility criteria, inability to complete follow-up, and deviation from the approved dose/regimen. As a result, 11 patients were included in the analysis set for the final study report.

Variables and data sources

Baseline Characteristics and General Information

1. Demographics (gender, race, and age)
2. Past medical history, prior treatments, and concomitant medications (including treatments and medications related to sAA, medical history of hematologic disorders, and treatments unrelated to sAA)
3. Physical examination and vital signs

4. Clinical laboratory results of interest: Complete blood count (CBC: hemoglobin, hematocrit, platelet count, absolute neutrophil count), liver function tests (LFT: aspartate transaminase [AST], alanine transaminase [ALT], and total/direct bilirubin)
5. Cataract evaluation
6. Eltrombopag administration including rabbit anti-thymocyte globulin (r-ATG) and CsA

Primary Endpoint

1. Incidence and severity of adverse events (AEs) and serious adverse events (SAEs)

Secondary Endpoint

1. Overall response rate (ORR) at 6 months, including complete response (CR) and partial response (PR), as determined by blood count assessments

Data were retrospectively extracted from the medical charts of patients diagnosed with sAA who were treated with eltrombopag based on the investigator's decision in accordance with locally approved prescribing information for sAA. All data were collected using an electronic case report form (e-CRF) developed by the designated contract research organization (CRO).

Statistical methods

Baseline Characteristics and General Information

Baseline characteristics and general information were summarized using descriptive statistics. For continuous variables, descriptive statistics included mean, standard deviation, median, minimum, and maximum values. For categorical variables, frequency and percentage were presented for each category.

Primary Endpoint

To assess the safety and tolerability of eltrombopag in combination with IST, the incidence of all AEs/adverse drug reactions (ADRs), SAEs/serious adverse drug reactions (SADRs), and unexpected AEs/ADRs were summarized. The overall AE summary included the number and percentage of patients experiencing the specific AE, along with the corresponding exact 95% confidence interval (CI). To identify factors that might affect safety outcomes, chi-square tests or Fisher's exact tests were performed.

Secondary Endpoint

To evaluate the efficacy of eltrombopag in combination with IST, hematologic response was assessed based on blood counts at 6 months or the closest time point within one month before or after 6 months (i.e., between 5 and 7 months from the analytical index date). Response rate and ORR were calculated. For patients who discontinued treatment before the 6-month time point, efficacy was assessed based on their last available data.

Results

This study was conducted to evaluate the safety, tolerability, and efficacy of eltrombopag in combination with IST in a real-world clinical setting among pediatric patients in Korea. A retrospective review was performed using 6-month data from the start of eltrombopag treatment, extracted from the medical charts (electronic medical records) of pediatric patients who received first-line eltrombopag in combination with r-ATG and CsA (IST). The study was conducted at a total of eight clinical sites in Korea. Among the 13 subjects enrolled at six of these sites, two were excluded due to violation of eligibility criteria, inability to complete follow-up, and deviation from the approved dose/regimen. As a result, 11 eligible subjects were included in the analysis population.

Regarding the demographic characteristics of the 11 subjects, 63.64% (7/11) were ‘male’ and 36.36% (4/11) were ‘female’. In terms of race, 90.91% (10/11) were ‘Korean’ and 9.09% (1/11) were classified as ‘Others’. The mean age was 10.09 (±4.74) years.

Analysis of AE incidence among the 11 subjects revealed a total of 19 AEs reported in 8 subjects (72.73%). Of these, two ADRs occurred in two subjects (18.18%), and both were classified as unexpected ADRs. Five SAEs were reported in 4 subjects (36.36%), all of which were unexpected SAEs, though none were classified as SADRs. Unexpected AEs occurred in 17 instances among 7 subjects (63.64%).

Among the 11 subjects, the most frequently reported AE based on preferred term (PT) was 'Pyrexia', which occurred in 27.27% (3/11 subjects, 3 cases). This was followed by 'Febrile neutropenia', 'Rash', and 'Hypertension', each reported in 18.18% (2/11 subjects, 3 cases, 2 cases, 2 cases), and 'Drug eruption', 'Hyperuricaemia', and 'Iron overload', each in 9.09% (1/11 subject, 1 case each). SAEs included 'Febrile neutropenia', 'Serum sickness', 'Bone infarction', and 'Renal failure', each reported in 9.09% (1/11 subject, 2 cases, 1 case, 1 case, 1 case). The most frequently reported unexpected AE was 'Pyrexia', at 27.27% (3/11 subjects, 3 cases), followed by 'Febrile neutropenia' and 'Hypertension', each in 18.18% (2/11 subjects, 3 cases, 2 cases), and 'Drug eruption', 'Hyperuricaemia', and 'Iron overload', each in 9.09% (1/11 subject, 1 case each). Unexpected SAEs included 'Febrile neutropenia', 'Serum sickness', 'Bone infarction', and 'Renal failure', each reported in 9.09% (1/11 subject, 2 cases, 1 case, 1 case, 1 case).

Among the 19 AEs reported in 11 subjects, the severity was classified as 'mild' and 'moderate' for 9 cases each, and 'severe' for 1 case. The outcomes were 'recovered' in 15 cases and ‘resolving’ in 4 cases. Causality with the study drug was assessed as 'unlikely' in 17 cases and 'definite' in 2 cases. For drugs other than the study drug, causality was assessed as 'concomitant medication' in 8 cases, 'underlying disease' in 2 cases, and 'other' in 2 cases. Actions taken on the study drug were 'dose not changed' in all 19 cases.

Among the 11 subjects, response was evaluated in 6 subjects who met the criteria for response assessment. Of the 6 subjects who met the response criteria, 'partial response (PR)' was observed in 50.00% (3/6 subjects), 'no response (NR)' in 33.33% (2/6 subjects), and 'complete response (CR)' in 16.67% (1/6 subjects). The ORR, including CR and PR, was 66.67% (4/6 subjects).

Interpretation

In this study, objective data were used to evaluate the safety and efficacy trends of eltrombopag in Korean pediatric patients with sAA, by classifying the data collection period into a baseline period and an observation period based on the analytical index date. Based on previous studies involving pediatric patients with sAA who received eltrombopag in combination with IST, the results of this study showed no new information or unusual patterns regarding the safety profile of eltrombopag, and no concerns were identified regarding its efficacy. Although the incidence of AEs and response rates were analyzed by baseline characteristics and general background factors, no variables showed statistically significant differences.

Conclusion

Through this observational study, the safety and efficacy of the combination therapy of IST and eltrombopag were confirmed in the real-world clinical setting in Korea. A comprehensive review of the safety and efficacy outcomes from this study revealed no significantly concerning AEs compared to existing prior studies and the approved labeling. No new safety information or unusual trends were observed in the safety profile of eltrombopag, and no concerns were identified regarding its efficacy.