Elapegademase in patients with ADA-SCID previously treated with pegademase: a case series

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Introduction

- In the rare autosomal recessive disorder adenosine deaminase severe combined immunodeficiency (ADA-SCID) deficient and impaired ADA activity leads to the accumulation of toxic levels of deoxyadenosine nucleotides (dAXP), causing depleted lymphocyte development and systemic metabolic manifestations
- Children with ADA-SCID usually die before 2 years of age, unless they are diagnosed early and effective treatment is initiated[1]
- Early intervention can support improvements in prognosis and quality of life[2]
- ADA enzyme replacement therapy (ERT) is typically used from diagnosis until patients can receive hematopoietic stem cell transplantation (HSCT) or gene therapy, or when HSCT and gene therapy are not available or effective, ERT may be continued long-term[3]
- Elapegademase-lvlr (REVCOVI®), a PEGylated recombinant ADA, is the only ERT approved by the US Food and Drug Administration (FDA) for ADA-SCID, replacing pegademase (Adagen®; PEGylated modified bovine ADA) in 2018[4]
- Two small Phase 3 trials have demonstrated the efficacy and safety of elapegademase for the treatment of ADA-SCID[2,5]
  - In a US trial involving seven patients transitioning from pegademase (NCT01420627), six patients completed 1.4–4.2 years of elapegademase therapy, during which ADA activity improved compared with pegademase, metabolic detoxification was maintained, lymphocyte counts improved or stabilized, and treatment was well tolerated. One patient withdrew after two doses of an early elapegademase formulation owing to injection-site pain caused by EDTA[2]
  - In a Japanese trial (JapicCTI-163204; N = 4), three patients who received elapegademase therapy for more than 3 years achieved sufficient and stable ADA activity and undetectable dAXP levels, increased T-and B-cell numbers, and experienced no elapegademase-related adverse events (AEs). One patient with severe pneumonia at enrollment died after 16 weeks of elapegademase therapy, despite increased ADA activity and dAXP detoxification[5]
- Longer-term, real-world effectiveness, and tolerability data for elapegademase in patients with ADA-SCID are of interest given the rarity of ADA-SCID

Objective

- The elapegademase registry study (NCT03878069) was conducted as a post-marketing requirement of the US FDA to bolster the available data on elapegademase safety and effectiveness in patients with ADA-SCID
- Here we report a case series of four patients from the elapegademase registry who initiated elapegademase in the aforementioned Phase 3 trial (NCT01420627) and who have up to 8 years of follow-up data

Methods

- The single-arm, open-label, US multicenter elapegademase registry study collected real-world data from patients with ADA-SCID receiving elapegademase treatment
- We analyzed prospective data from a case series comprising the patients who transitioned from prior treatment with pegademase to elapegademase in the US Phase 3 trial and continued elapegademase treatment in the registry for at least 2 years
- Assessments included plasma ADA activity, erythrocyte dAXP levels, clinical and immunological status, and safety parameters
- Patients received elapegademase treatment during routine clinical care; optimal dosage was established by treating physicians for individual patients
- The recommended assessment schedule (based on the US elapegademase prescribing information) could be modified by treating physicians according to their standard practice and evaluation of individual patient needs
- Owing to the variable timing of clinical assessments in real-world practice, data are limited for some of the reported assessment points

Limitations

- This analysis is of a small case series of four patients
- Real-world data collection is variable; data on patients' immune function are sparse and inconsistent

Results

Patient overview

- This analysis included data from the four patients (from four US sites) who transitioned from pegademase to elapegademase treatment for ADA-SCID in the US Phase 3 trial (February 2015–May 2019) and continued receiving treatment in the US registry (April 2019–January 2023)
- Among the four patients:
  - two were diagnosed with ADA-SCID in infancy (both male) and two were diagnosed in early childhood (both female)
  - all initiated ERT with pegademase within 1 year of their diagnosis
  - one patient continued ERT after unsuccessful gene therapy; HSCT was not an option for the other three patients
  - duration of pegademase treatment prior to Phase 3 trial entry ranged from 15 to 25 years, with a further 1.2 months of exposure before transitioning to elapegademase
  - mean patient age at first elapegademase initiation was 21 years (range, 16–31 years)
- Total mean (standard deviation) duration of elapegademase treatment for these patients across the combined Phase 3 trial and registry periods was 5.8 (1.9) years (range, 3.3–7.9 years)
- These four patients received elapegademase doses of 0.08–0.31 mg/kg/week. Two patients required dose adjustments based on clinical assessments
  - Elapegademase dose was reduced for patient 1, from 10 mg/week (0.19 mg/kg/week) during the Phase 3 trial, to 9.6 mg/week (0.18 mg/kg/week) at registry entry, and 4.5 mg/week (0.08 mg/kg/week) after 16 months in the registry
  - Patients 2 and 3 maintained the same doses throughout the Phase 3 trial and registry periods (13.3 and 14.8 mg/week [0.29 and 0.17 mg/kg/week], respectively)
  - The dose was increased for patient 4, from 10 mg/week (0.21 mg/kg/week) during the Phase 3 trial, to 12 mg/week (0.26 mg/kg/week) at registry entry, and 14.4 mg/week (0.31 mg/kg/week) after 33 months in the registry

Summary of effectiveness outcomes

- All four patients maintained satisfactory levels of both ADA activity and dAXP during their respective periods of elapegademase treatment (**Figure 1**)
  - At registry end, ADA activity levels were numerically higher than at elapegademase baseline, and also exceeded levels recorded at the end of the Phase 3 trial
  - All four patients were considered metabolically detoxified owing to maintenance of satisfactory dAXP levels (≤ 0.02 mmol/L)
- Lymphocyte counts were stable throughout the combined period studied, although data for lymphocyte subsets were limited (**Figure 1**)
- During the Phase 3 trial period, two patients were hospitalized three times; during the registry study period, two patients experienced five hospitalizations, each of which lasted between 4 and 26 days (**Figure 1**)

Summary of safety outcomes

- During the Phase 3 trial period, the four patients experienced a total of 13 infections; most of these were mild, but two necessitated hospitalization (**Figure 1**)
- During the registry study period, three patients experienced eight infections that resolved without sequelae and required no treatment interruption; infection rates remained constant throughout the registry study period (**Figure 1**)
  - Four (of the eight) infections were COVID-19 infections, of which three were mild and one was moderate in severity
- No patients experienced any elapegademase-related AEs

Conclusions

- This case series provides reassuring evidence of the long-term tolerability and effectiveness of elapegademase treatment
  - Patients treated with elapegademase achieved sufficient, stable plasma ADA activity levels and maintained metabolic detoxification and total lymphocyte counts for up to 8 years
  - Hospitalization and infection rates were stable
  - Variability on all measures was seen, but overall, patients did not deteriorate during elapegademase treatment
- This cohort received long-term ERT for ADA-SCID, with up to 30 years of treatment, remaining clinically stable without any new safety concerns

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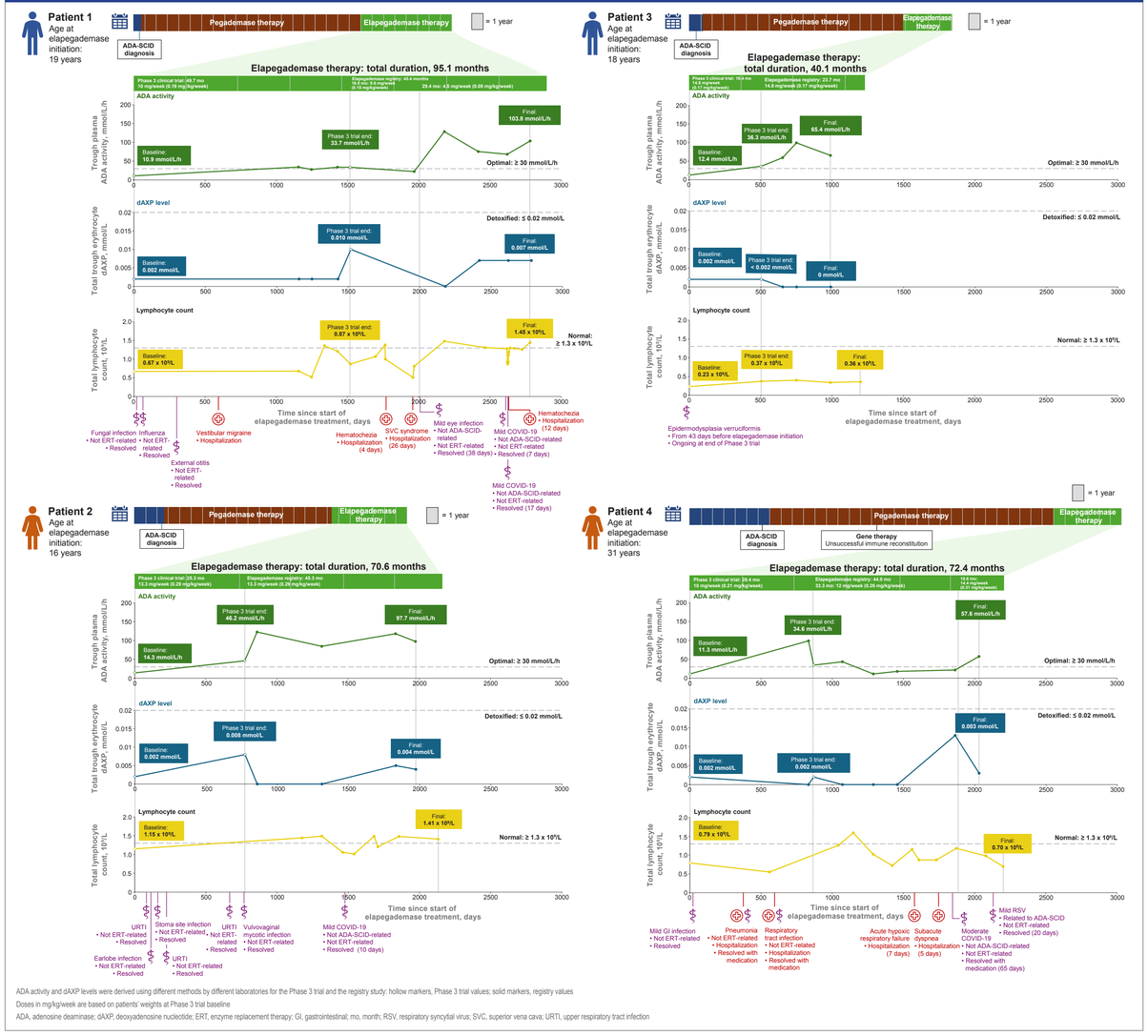
Figure 1. Patient profiles



ADA activity and dAXP levels were derived using different methods by different laboratories for the Phase 3 trial and the registry study: hollow markers, Phase 3 trial values; solid markers, registry values

Doses in mg/kg/week are based on patients' weights at Phase 3 trial baseline

ADA, adenosine deaminase; dAXP, deoxyadenosine nucleotide; ERT, enzyme replacement therapy; GI, gastrointestinal; mo, month; RSV, respiratory syncytial virus; SVC, superior vena cava; URTI, upper respiratory tract infection