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Emapalumab in patients with primary hemophagocytic lymphohistiocytosis: Efficacy and safety outcomes from a multinational, open-label, single-arm study

Franco Locatelli,[1] Ahmed Naqvi,[2] Beki James,[3] Julián Sevilla,[3,4] Simone Cesaro,[5] Stephan Ehl,[6] Didier Halimi,[7] Emmanuel Monnet,[7] Ben Peace,[8] Veronica Asnaghi,[7] Cristina de Min,[7] Michael Jordan[9]

[1] Ospedale Pediatrico Bambino Gesù, Catholic University of the Sacred Heart, Rome, Italy; [2]The Hospital for Sick Children, Toronto, Canada; [3]Leeds Children's Hospital, Leeds, United Kingdom; [4]Hospital Universitario Niño Jesús Servicio de Hemato-Oncología Pediátrica, Madrid, Spain; [5]Ospedale della Donna e del Bambino, U.O.C. Oncoematologia Pediatrica, Verona, Italy; [6]Freiburg University Medical Center, Faculty of Medicine, Institute for Immunodeficiency, Center for Chronic Immunodeficiency, Freiburg, Germany; [7]Sobi, Basel, Switzerland; [8]Sobi, Stockholm, Sweden; [9]University of Cincinnati College of Medicine, Department of Pediatrics, Cincinnati, United States of America

CONCLUSIONS

- Patients with primary hemophagocytic lymphohistiocytosis (HLH) treated with emapalumab are associated with an overall response rate exceeding 60%, allowing 71.4% of study participants to achieve the clinical stability necessary to receive potentially curative hematopoietic stem cell transplant (HSCT) or reaching study end alive, while maintaining a favorable safety profile.
- Glucocorticoid dosing was reduced by more than half for >40% of participants.
- These outcomes are consistent with earlier observations of patients with primary HLH treated with emapalumab in a previous clinical trial and in real-world clinical practice.

INTRODUCTION

- Primary HLH is a rare, life-threatening disorder characterized by immune dysregulation and hyperinflammation driven by excessive interferon-gamma (IFNγ) levels.[1,2]
- Allogeneic HSCT is the only potentially curative treatment.[3]
- Emapalumab, an anti-IFNγ monoclonal antibody that binds free and receptor-bound IFNγ,[4] has demonstrated efficacy in controlling hyperinflammation in patients with primary HLH before undergoing HSCT[5] and is approved by the US Food and Drug Administration (FDA) for the treatment of adult and pediatric patients with primary HLH with refractory, recurrent or progressive disease or intolerance with conventional therapy.[6]

OBJECTIVE

- To further investigate the efficacy and safety of emapalumab for treating patients with primary HLH in treatment-naïve and treatment-experienced settings and evaluate a 3 mg/kg starting dose.

METHODS

Study Design

- Study NI-0501-09 was an open-label, single-arm, phase 3 study of emapalumab for the treatment of primary HLH conducted across 7 countries (Canada, Germany, Italy, Spain, Switzerland, United Kingdom, and the United States).
- Patients were administered an initial intravenous infusion of emapalumab 3 mg/kg with subsequent infusions twice weekly; Investigators could increase dosing to 6 or 10 mg/kg in case of unsatisfactory response.

Eligibility Criteria

- Males and females diagnosed with primary HLH between the time of birth and 18 years of age, with active HLH disease.
- A molecular diagnosis of primary HLH, familial history consistent with primary HLH, or fulfilment of the HLH-2004 definition of HLH wherein 5 of the following 8 criteria were met:
  - Fever;
  - Splenomegaly;
  - Cytopenias affecting 2 of 3 lineages in the peripheral blood (hemoglobin <90 g/L; platelets <100 × 10^9/L; neutrophils <1 × 10^9/L);
  - Hypertriglyceridemia (fasting triglycerides ≥3 mmol/L or ≥265 mg/dL) and/or hypofibrinogenemia (≤1.5 g/L);
  - Hemophagocytosis in bone marrow, spleen, or lymph nodes, with no evidence of malignancy;
  - Low or absent natural killer-cell activity;
  - Ferritin ≥500 µg/L;
  - Soluble CD25 (sCD25; also known as soluble interleukin-2 receptor α) ≥2400 U/mL.
- Patients with secondary HLH, malignancy or any other concomitant disease were excluded.

Endpoints

- Overall response (achievement of either complete or partial response or HLH improvement) at end of treatment or Week 8 (whichever occurred earlier) in the all-treated analysis set.
  - A 1-sided exact binomial test was used to compare the proportion of patients with overall response to a hypothesized null hypothesis of at most 40%.
- Time to response.
- Duration of response.
- Overall response at start of conditioning (or at last emapalumab infusion, if HSCT was not performed).
- Number of patients able to reduce glucocorticoids by ≥50% versus baseline during emapalumab treatment.
- Survival to HSCT.
- Overall survival.
- Number of patients able to proceed to HSCT, when deemed indicated.
- Safety and tolerability were also monitored.
- Biomarkers of IFNγ activity, including chemokine C-X-C motif ligands-9 and -10 (CXCL9/CXCL10) and hyperinflammation (sCD25).

RESULTS

Baseline Characteristics

- 35 patients with primary HLH were enrolled in the study between February 2019 and September 2022.
- The majority of patients were infants/toddlers, male and White.
- Genetic confirmation of primary HLH was available for 26 (74.3%) patients and 10 patients (28.6%) had a family history of primary HLH (**Table 1**).
- Sixteen (45.7%) patients were treatment-naïve and 19 (54.3%) were treatment-experienced.
- Prior treatments for HLH administered to treatment-experienced patients included:
  - Etoposide (n=13 [76.5%])
  - Immune sera/immunoglobulins (n=3 [15.8%])
  - Anakinra (n=2 [11.8%])
  - Ruxolitinib (n=1 [5.9%])
  - Tocilizumab (n=1 [5.9%])
  - An unspecified interleukin inhibitor (n=1 [5.9%]).

Table 1: Baseline characteristics (all-treated analysis set)

	Total (N=35)
Age, years, median (range) At HLH diagnosis	0.3 (0–17)
Age group, n (%)	
Newborns (0–27 days)	5 (14.3)
Infant/Toddler (28 days–2 years)	22 (62.9)
Child (2–11 years)	6 (17.1)
Adolescent (12–18 years)	2 (5.7)
Sex, male, n (%)	21 (60.0)
Race, n (%)	
White	18 (51.4)
Black or African-American	4 (11.4)
Asian	4 (11.4)
American Indian or Alaska Native	1 (2.9)
Native Hawaiian or other Pacific Islander	1 (2.9)
Unknown	7 (20.0)
Genetic confirmation of HLH[a], n (%)	26 (74.3)
PRF1	12 (34.3)
UNC13D	8 (22.9)
RAB27A	4 (11.4)
STXBP2	4 (11.4)
Caspases, *TAP2*[b]	1 (2.9)
Family history of primary HLH, n (%)	10 (28.6)

[a]Patients could have more than 1 mutation; therefore, the number of mutations does not sum up to the number of patients with genetic confirmation;
[b]Mutation detected in concomitance with heterozygous mutation in *UNC13D* gene.
HLH, hemophagocytic lymphohistiocytosis.

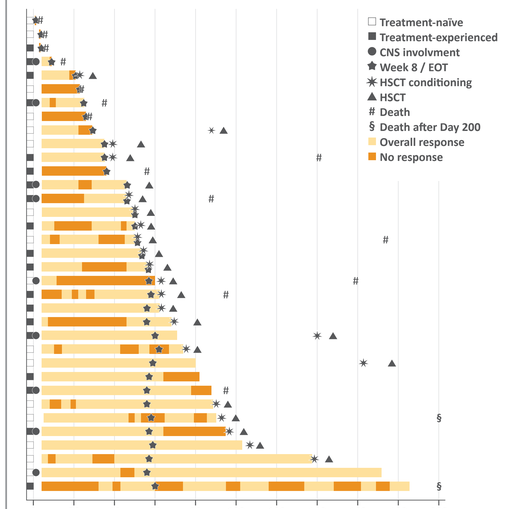
Efficacy

- Overall response rate in the all-treated analysis set was 62.9% (*P*=0.0053 vs null hypothesis).
  - Median time to response was 4 days.
- Overall, 28 patients (80% of the all-treated analysis set) experienced at least 1 response that was maintained for at least 4 days at any time during the study.
- At study end, 25 (71.4%) participants had undergone HSCT, or were alive if HSCT was not deemed indicated by the investigators (**Figure 1**).
- Of the 23 patients who underwent HSCT during the study, 17 (73.9%) were alive at study end.
- 15 patients (42.9%) had reduced glucocorticoid dosing by ≥50% versus baseline at end of treatment.
- Similar responses were observed in patients who were treatment-naïve and treatment-experienced.

Safety

- At least 1 treatment-emergent adverse event (TEAE) was reported by all 35 patients (**Table 2**).
- The most common TEAEs (≥20% patients) were pyrexia, vomiting, condition aggravated, diarrhea, hypertension, pain, rash, abdominal pain, tachycardia, and hypokalemia (**Table 3**).
- The majority of TEAEs were mild or moderate in severity, but 129 serious TEAEs were reported in 32 (91.4%) patients.
- Study drug was discontinued by 7 (20.0%) patients as a result of 10 TEAEs.
  - All TEAEs leading to discontinuation were severe in intensity and related to aggravation of the patients' clinical condition.
- Thirty drug-related TEAEs were reported by 9 (25.7%) patients.
- A total of 6 serious drug-related TEAEs were experienced by 4 (11.4%) patients.
  - Study drug was discontinued in one patient.
  - The incidence of drug-related serious TEAEs was similar in treatment-naïve and treatment-experienced patients.
- Thirteen infusion-related reactions were reported in 7 (20.0%) patients, 2 of which were serious.
- 125 infection TEAEs were observed in 29 (82.9%) patients; most were mild in intensity.
- No serious hypersensitivity reactions, such as anaphylactic or anaphylactoid reactions were reported.
- When anti-drug antibodies were observed (n=2), they were non-neutralizing with no apparent effect on the efficacy, safety or pharmacologic properties of emapalumab.
- There were 21 serious TEAEs associated with an outcome of death in 16 (45.7%) patients, none of which were assessed as drug-related.
  - 8 patients died within 2 weeks of last emapalumab infusion (treatment duration was 1–8 days in 4 patients); 2 patients died 24 days and 3.6 months, respectively, after last emapalumab infusion.
  - 6 patients died after emapalumab treatment was completed and patients had undergone HSCT.
  - The incidence of serious TEAEs with an outcome of death was similar in treatment-naïve and treatment-experienced patients.

Figure 1: Overview of the duration of treatment and overall response for patients administered emapalumab (all-treated analysis set)



Survival

- After median follow-up of 9.38 (range, 0.1–23.3) months, 19 (54.3%) patients were alive (**Figure 1**).
- Median overall survival time was not estimable (not yet reached).
- Estimated 3-, 6-, and 12-month survival was 74%, 60%, and 54%, respectively, in the all patients all-treated analysis.

Biomarkers

- Mean serum CXCL10 and CXCL9 levels decreased by approximately 4- and 7-fold, respectively, from baseline to end of treatment or Week 8 (mean CXCL10 levels decreased from 14,195 ng/L to 3203 ng/L, and CXCL9 decreased from 14,114 ng/L to 2109 ng/L).
- Mean serum levels of sCD25 approximately halved from 17,026 ng/L at baseline to 9883 ng/L at end of treatment or Week 8.

Table 2: Adverse events (all-treated analysis set)

N=35	Events	n (%)
TEAEs, n (%)	696	35 (100)
Treatment-related, n (%)	30	9 (25.7)
TEAES by severity, n (%)		
Mild	415	30 (85.7)
Moderate	174	27 (77.1)
Severe	107	31 (88.6)
SAEs, n (%)	129	32 (91.4)
Treatment-related, n (%)	6	4 (11.4)
Infection TEAEs, n (%)	125	29 (82.9)
Mild	64	21 (60.0)
Moderate	33	15 (42.9)
Severe	28	16 (45.7)
Infusion-related reactions	13	7 (20.0)
TEAEs leading to discontinuation, n (%)	10	7 (20.0)
TEAEs with an outcome of death, n (%)	21	16 (45.7)

SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Table 3: TEAEs observed in ≥20% of patients

N=35	Events	n (%)
Pyrexia	32	17 (48.6)
Vomiting	25	17 (48.6)
Condition aggravated	15	15 (42.9)
Diarrhea	21	13 (37.1)
Hypertension	11	11 (31.4)
Pain	15	9 (25.7)
Rash	13	8 (22.9)
Abdominal pain	12	8 (22.9)
Hypokalemia	7	7 (20.0)
Tachycardia	7	7 (20.0)

SAE, serious adverse event; TEAE, treatment-emergent adverse event.

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References
1. Meeths M, et al. *Pediatr Blood Cancer* 2015;62:346–352; 2. Jordan MB, et al. *Blood* 2011;118:4041–4052; 3. Lehmberg K, et al. *Front Pediatr* 2019;7:435. 4. Hatterer E, et al. *Cytokine* 2012;59:570; 5. Locatelli F, et al. *N Engl J Med* 2020;382:1811–1822; 6. GAMIFANT (emapalumab-lzsg). Prescribing information. 2019.

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