gamifant®
emapalumab-lzsg

*Primary HLH (XLP1) with EBV*

Introducing a real primary HLH patient case

# Mack's journey

The diagnosis and management of primary hemophagocytic lymphohistiocytosis (HLH) in an adolescent patient presenting with Epstein-Barr virus (EBV)

*The details presented in this case are true and have been shared with the permission of the patient and/or caregiver to help broaden the healthcare community's knowledge of this rare condition. This case represents one patient's experience and the clinical judgment of one treatment team. Individual results may vary.*

XLP1=X-linked lymphoproliferative disease.

## Indication

Gamifant® (emapalumab-lzsg) is an interferon gamma (IFNγ)–blocking antibody indicated for the treatment of adult and pediatric (newborn and older) patients with primary hemophagocytic lymphohistiocytosis (HLH) with refractory, recurrent, or progressive disease or intolerance with conventional HLH therapy.

## Important Safety Information

### Infections

Before initiating Gamifant, patients should be evaluated for infection, including latent tuberculosis (TB). Prophylaxis for TB should be administered to patients who are at risk for TB or known to have a positive purified protein derivative (PPD) test result or positive IFNγ release assay.

**Please see Important Safety Information on page 8. Click here for full Prescribing Information for Gamifant, including Patient Information.**

# Overview

## JANUARY 2020

Mack was admitted to the emergency room and diagnosed with EBV. When his symptoms worsened, Mack's treatment team began to suspect that primary HLH could be responsible.

This case study details the factors that contributed to a confirmed diagnosis of primary HLH and the treatment plan that conditioned Mack for hematopoietic stem cell transplantation (HSCT).

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### Infections

During Gamifant treatment, patients should be monitored for TB, adenovirus, Epstein-Barr virus (EBV), and cytomegalovirus (CMV) every 2 weeks and as clinically indicated.

Patients should be administered prophylaxis for herpes zoster, *Pneumocystis jirovecii*, and fungal infections prior to Gamifant administration.

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## **Day 1:** Initial presentation

*January 12, 2020*

### 15-year-old male presents to hospital with symptoms consistent with EBV

- Headache
- Fever
- Nausea and vomiting
- Lymphadenopathy

**Mack is discharged from the hospital but returns 1 week later with worsening symptoms.**

EBV is a documented trigger of HLH. It is believed that EBV-infected B cells stimulate cytotoxic T lymphocytes leading to hypercytokinemia and stimulation of histolytic cells.[1,2]

## Important Safety Information

### Increased Risk of Infection With Use of Live Vaccines

Do not administer live or live attenuated vaccines to patients receiving Gamifant and for at least 4 weeks after the last dose of Gamifant. The safety of immunization with live vaccines during or following Gamifant therapy has not been studied.

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# Differential diagnosis

## Day 7

*January 19, 2020*

**Mack is admitted to the ICU. Based on his symptoms, a hematologist/oncologist is consulted, primary HLH is suspected, and a series of tests is performed.**

- Lab values including blood counts, liver enzymes, and electrolytes suggest primary HLH
- HLH-2004 criteria are used to evaluate Mack's symptoms; most criteria are met

**Based on fulfillment of the HLH-2004 criteria, primary HLH is diagnosed and treatment is initiated.** Mack is transferred to another hospital where a blood and bone marrow transplant specialist assumes his care.

## Days 10-30

**Additional testing is performed to help confirm the clinical diagnosis of primary HLH and identify underlying triggers.**

*January 22, 2020*

- Viral polymerase chain reaction (PCR) test
- Flow cytometry on perforin/granzyme B, signaling lymphocytic activation molecule (SLAM)-associated protein (SAP), X-linked inhibitor of apoptosis protein (XIAP), CD107A, and genetic testing for mutations associated with primary HLH

*January 28, 2020*

- Lumbar puncture

*February 5, 2020*

- Cytokine and CXCL9 measurement

## Day 41

*February 22, 2020*

**Flow cytometry and genetic testing results confirm primary HLH triggered by XLP1,** a genetic disorder characterized by extreme vulnerability to EBV.

## Day 84

*April 5, 2020*

**Imaging tests are performed to rule out possible malignancies.**

- Computed tomography (CT) scan of chest, abdomen, and pelvis

EBV has been reported to present concurrently with lymphoma. It is critical to screen patients for possible malignancies since lymphoma may share a similar presentation with HLH.[3]

## Important Safety Information

### Infusion-Related Reactions

Infusion-related reactions, including drug eruption, pyrexia, rash, erythema, and hyperhidrosis, were reported with Gamifant treatment in 27% of patients. In one-third of these patients, the infusion-related reaction occurred during the first infusion.

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# Patient lab values

- SAP (deficient in EBV and XLP1 patients) undetectable
- EBV present in bone marrow cells

## Mack exhibits most of the HLH-2004 diagnostic criteria

*(5 out of 8 are required for diagnosis)*

- ✓ Fever
- ✓ Hypertriglyceridemia (fasting) ≥265 mg/dL and hypofibrinogenemia 1.2 g/L
- ✓ Splenomegaly
- ✓ Hemophagocytosis observed in bone marrow cells
- ✓ Pancytopenia: Hemoglobin <90 g/L | Platelets <100 x $10^9$/L | Neutrophils <1.0 x $10^9$/L
- ✓ Ferritin 4300 µg/L
- ✓ Soluble CD25 levels elevated

## Results of genetic testing and additional screening support primary HLH diagnosis

- Flow cytometry identifies XLP deficiency
- Genetic testing confirms XLP1 by mutation in *SH2D1A* gene
- CXCL9 testing showed abnormally high cytokine levels
- EBV PCR in the plasma was positive (>100,000 IU/mL)
- Lumbar puncture reveals no evidence of central nervous system (CNS) HLH
- CT scan of chest, abdomen, and pelvis revealed no abnormalities or malignancies

## Important Safety Information

### Adverse Reactions

In the pivotal trial, the most commonly reported adverse reactions (≥10%) for Gamifant included infection (56%), hypertension (41%), infusion-related reactions (27%), pyrexia (24%), hypokalemia (15%), constipation (15%), rash (12%), abdominal pain (12%), CMV infection (12%), diarrhea (12%), lymphocytosis (12%), cough (12%), irritability (12%), tachycardia (12%), and tachypnea (12%).

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# Treatment journey

**Day 16** | *January 28, 2020*

**Dexamethasone is initiated at a starting dose of 10 mg/m² per day.**

- Rituximab was also administered

**Day 19** | *January 31, 2020*

**Etoposide is initiated at a starting dose of 150 mg/m² concomitantly with dexamethasone.**

- Multiple blood transfusions were administered to mitigate HLH-induced cytopenias and the effects of chemotherapy on platelet count
- Treatment was considered partially successful; Mack's fever resolved and he was able to leave the ICU, but disease activity remained significant and many symptoms were still present
- Very high levels of soluble CD25, ferritin, cytokines, and CXCL9 expression prompted the team to explore a more targeted treatment option
- Toxicity concerns mounted with continuous steroid and chemotherapy use
- Mack's last dose of chemotherapy is received on March 3 and is not restarted

**Day 26** | *February 7, 2020*

**Dexamethasone is tapered to a dose of 5 mg/m².**

**Day 33** | *February 14, 2020*

**Gamifant is initiated at a starting dose of 150 mg (2.7 mg/kg) 2x weekly.***

*The recommended starting dosage of Gamifant is 1 mg/kg as an intravenous infusion over 1 hour, twice per week. Subsequent doses may be increased based on clinical and laboratory criteria.[4]

**Day 40** | *February 21, 2020*

**Dexamethasone is tapered to a dose of 2.25 mg/m².**

**Gamifant infusions drop to 1x weekly as HLH signs improve.***

**Day 68** | *March 20, 2020*

**CNS complications arise; Gamifant is titrated up to a 2x weekly dose of 300 mg (4.6 mg/kg) in response.**

- Peripheral markers of HLH began to improve and normalize
- The dose of Gamifant was increased in response to optic nerve vasculitis
- Intrathecal therapy (methotrexate and hydrocortisone) is initiated and given weekly

**Mack begins to experience improvement in his optic nerve vasculitis.**

**Day 108 and 121**

*April 29, 2020 and May 12, 2020*

**Cyclophosphamide is administered at a dose of 1 g/m².**

**Day 122** | *May 13, 2020*

**In preparation for allogeneic HSCT, Mack continues to receive Gamifant, intrathecal therapy, and low doses of dexamethasone.**

- Mack receives his last Gamifant infusion on June 7, the day before the procedure

**Day 148** | *June 8, 2020*

**After conditioning, Mack successfully undergoes HSCT.**

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Additional selected adverse reactions (all grades) that were reported in less than 10% of patients treated with Gamifant included vomiting, acute kidney injury, asthenia, bradycardia, dyspnea, gastrointestinal hemorrhage, epistaxis, and peripheral edema.

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# Clinical response

## Day 40

*February 21, 2020*

**1 week after Gamifant is initiated, Mack's condition stabilizes.**

- Primary HLH symptoms, including fever, resolve
- Normalization of liver markers and liver function, coagulation, and levels of ferritin, soluble CD25, and CXCL9 are observed
- Transfusion independence is achieved
- EBV resolves

## Days 240-270

*September-October 2020*

**3 months following transplantation, Mack's condition remains stable.**

- HLH parameters (soluble CD25, CXCL9, etc)—*normal*
- Chimerism blood test reveals 100% donor cells are achieved by 30 days post transplant
- SAP levels—*normal*
- Organ function—*normal*

**Mack resumes activities, including sports and travel.**

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# Thank you for reviewing Mack's case

**Diagnosing primary HLH can be challenging.**

**Visit *Gamifant.com* to learn more about primary HLH and Gamifant.**

**If you'd like to consult a primary HLH treatment expert, contact your local Sobi Health Systems Director.**

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**References: 1.** Hashemi-Sadraei N, Vejpongsa P, Baljevic M, Chen L, Idowu M. Epstein-Barr virus-related hemophagocytic lymphohistiocytosis. Hematologic emergency in the critical care setting. *Case Rep Hematol*. 2015;2015:491567. doi:10.1155/2015/4915672015 **2.** Gourdarzipour K, Kajiyazdi M, Mahdaviyani A. Epstein-Barr virus-induced hemophagocytic lymphohistiocytosis. *Int J Hematol Oncol Stem Cell Res.* 2013;7(1):42-45. **3.** Ricard JA, Charles R, Tommee CG, Yohe S, Bell WR, Flanagan ME. Epstein virus Barr-positive diffuse large B-cell lymphoma associated with hemophagocytic lymphohistiocytosis. *J Neuropathol Exp Neurol*. 2020;79(8): 915-920. doi:10.1093/jnen/nlaa061 **4.** Gamifant (emapalumab-lzsg) prescribing information. Stockholm, Sweden: Sobi, Inc. 2022.

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