gamifant®
emapalumab-lzsg

IFNγ and CXCL9 in primary HLH

Explore the relationship between IFNγ, a key mediator of hyperinflammation, and CXCL9, a recognized biomarker of IFNγ activity that is associated with primary hemophagocytic lymphohistiocytosis (HLH).[1]

CXCL9=chemokine (C-X-C motif) ligand 9;
IFNγ=interferon gamma.

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.

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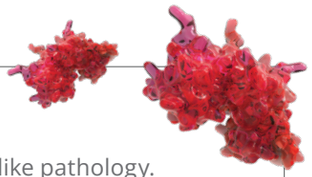
Primary HLH is rapidly progressive and often fatal[2]

This rare, hyperinflammatory condition of immune dysregulation is characterized by[3]:

IFNγ-activated macrophages that release an uncontrolled surge of proinflammatory cytokines[3]

Hyperinflammation that quickly becomes life-threatening[3]



The critical role of IFNγ

IFNγ was found to be essential for the development of HLH-like pathology. In murine models, inhibition of this cytokine led to an improvement of known features of HLH, including[4,5]:

- Increased blood cell counts (hemoglobin, platelets, and/or neutrophils)
- Reduction of triglyceride and ferritin levels
- Normalization of histopathological features of the spleen
- Reduction of macrophage activation, as evidenced by the reduction of hemophagocytosis in the liver

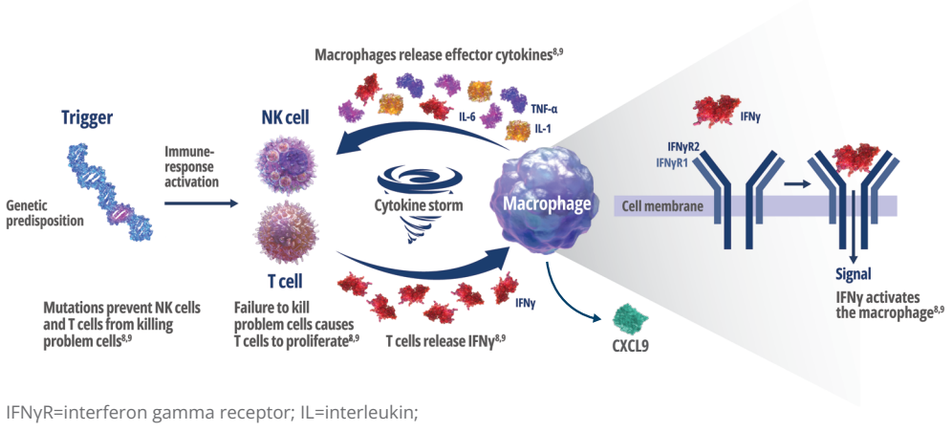
Diagnostic challenges[1,2]

In primary HLH, heterogeneous presentation of nonspecific signs and symptoms can delay a diagnosis. CXCL9 testing to evaluate IFNγ levels in patients may help uncover the source of their hyperinflammatory symptoms.

IFNγ is a central driver of hyperinflammation[6]

IFNγ is a key cytokine in the immune system. It plays an important role in cell communication during immune responses. In primary HLH, the immune system is dysregulated—and IFNγ contributes directly to the rapidly progressive and life-threatening symptoms of untreated primary HLH. Massive overexpression of IFNγ leads directly to downstream hypercytokinemia and hyperinflammation.[4,6,7]

CXCL9 is secreted in response to IFNγ, attracting T cells into inflamed tissues[7]



IFNγR=interferon gamma receptor; IL=interleukin;
NK=natural killer; TNF-α=tumor necrosis factor alpha.

1| In primary HLH, genetic defects disrupt immune function by preventing the cell lysis function of NK and T cells[6,8,9]

2| Impaired T cell function leads to proliferation of T cells and the release of a high volume of IFNγ[6,8,9]

3| IFNγ binds to macrophages, activating the release of downstream effector cytokines in addition to more IFNγ—perpetuating the cycle of hyperinflammation[6,8,9]

4| Cytokines involved in this severe, hyperinflammatory response are responsible for the clinical and laboratory features of primary HLH[6,8,9]

CXCL9: A marker for IFNγ activity[1]

Another type of cytokine, CXCL9, is a chemokine uniquely induced almost entirely by IFNγ, which causes T cells to move toward inflammation.[7] Evidence suggests that levels of CXCL9 reflect IFNγ production, as well as the degree of activation of IFNγ-induced signaling pathways. Because of this, CXCL9 testing can be useful both as an ancillary diagnostic tool and as a marker of treatment response.[1,2] Patients treated prior to CXCL9 testing may exhibit lower CXCL9 levels in their test results.[10] CXCL9 testing should be done as soon as possible to help inform treatment decisions.

CXCL9 testing sites

There is growing recognition of testing for CXCL9 as a biomarker for IFNγ activity.[2] The following organizations offer CXCL9 testing to help with identifying primary HLH in your patients:

Machaon Diagnostics	
Website	www.machaondiagnostics.com/test/cxcl9-level
Turnaround time	STAT: <24 hours Routine: <1 week
Lab hours	24/7
Phone	1-800-566-3462 510-839-5600
Fax	510-839-6153

MACHAON DIAGNOSTICS

Click here to learn more

Cincinnati Children's Hospital	
Website	www.testmenu.com/cincinnatichildrens/Tests/723501
Turnaround time	4 days
Lab hours	Mon-Fri, 8:00 AM to 5:00 PM (EST)
Phone	513-636-4685
Fax	513-636-3861

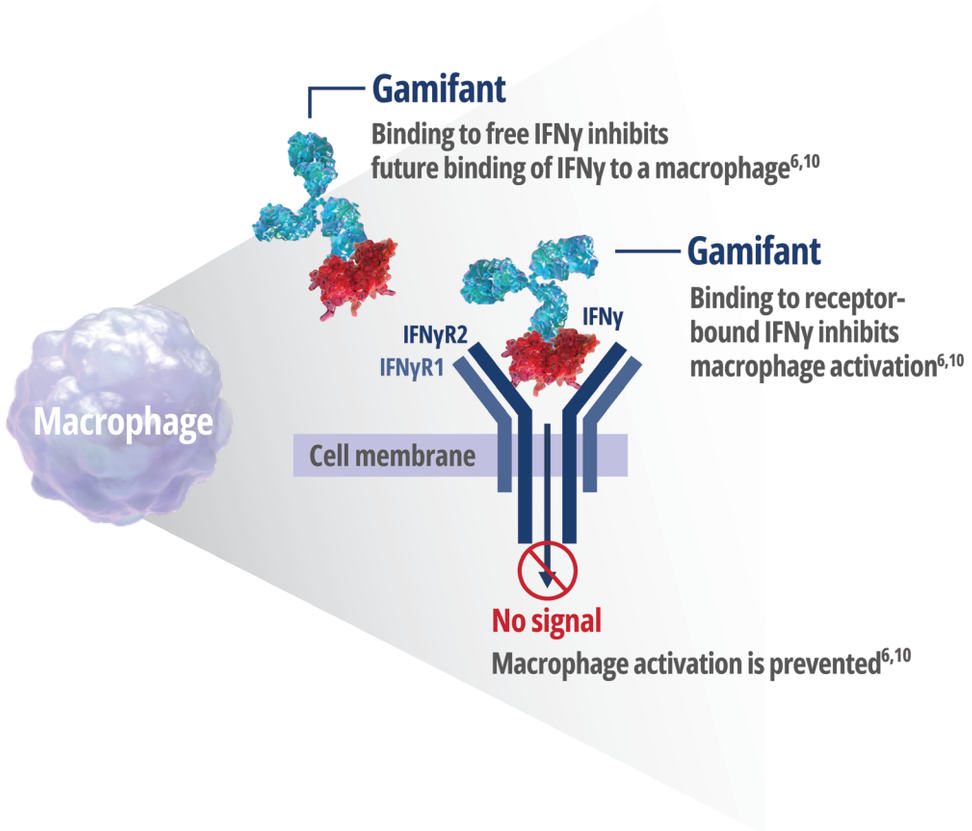
Cincinnati Children's®

Click here to learn more

Disclaimer: This is not an exhaustive list of labs offering CXCL9 testing, as additional labs continue to build new capabilities. Please check for the availability of this test within your own institution prior to contacting these sites.

Target and neutralize IFNγ

The first and only FDA-approved treatment for primary HLH, Gamifant is a monoclonal antibody that binds with affinity to **free** and **receptor-bound** IFNγ.[10,11]



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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.

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.

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.

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%).

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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TO LEARN MORE

about diagnosis and if Gamifant may be appropriate for your patients, please visit:

Gamifant.com

References: 1. De Benedetti F, Prencipe G, Bracaglia C, Marasco E, Grom AA. Targeting interferon-γ in hyperinflammation: opportunities and challenges. *Nat Rev Rheumatol*. 2021;17(11):678-691. doi:10.1038/s41584-021-00694-z **2.** Jordan MB, Allen CE, Weitzman S, Filipovich AH, McClain KL. How I treat hemophagocytic lymphohistiocytosis. *Blood*. 2011;118(15):4041-4052. doi:10.1182/blood-2011-03-278127 **3.** La Rosée P. Alleviating the storm: ruxolitinib in HLH. *Blood*. 2016;127(13):1626-1627. doi:10.1182/blood-2016-02-697151 **4.** Prencipe G, Caiello I, Pascarella A, et al. Neutralization of IFN-γ reverts clinical and laboratory features in a mouse model of macrophage activation syndrome. *J Allergy Clin Immunol*. 2018;141(4):1439-1449. doi:10.1016/j.jaci.2017.07.021 **5.** Di Cola I, Ruscitti P, Giacomelli R, Cipriani P. The pathogenic role of interferons in the hyperinflammatory response on adult-onset Still's disease and macrophage activation syndrome: paving the way towards new therapeutic targets. *J Clin Med*. 2021;10(6):1164. doi:10.3390/jcm10061164 **6.** Morimoto A, Nakazawa Y, Ishii E. Hemophagocytic lymphohistiocytosis: pathogenesis, diagnosis, and management. *Pediatr Int*. 2016;58(9):817-825. doi:10.1111/ped.13064 **7.** Cincinnati Children's. From the Clinical Laboratories of the Cancer & Blood Diseases Institute. CXCL9. Published Winter 2019. **8.** Price B, Lines J, Lewis D, Holland N. Haemophagocytic lymphohistiocytosis: a fulminant syndrome associated with multiorgan failure and high mortality that frequently masquerades as sepsis and shock. *S Afr Med J*. 2014;104(6):401-406. doi:10.7196/samj.7810 **9.** Sepulveda F, de Saint Basile G. Hemophagocytic syndrome: primary forms and predisposing conditions. *Curr Opin Immunol*. 2017;49:20-26. doi:10.1016/j.coi.2017.08.004 **10.** Gamifant (emapalumab-lszg) prescribing information. Stockholm, Sweden: Sobi, Inc. 2022. **11.** FDA approves first treatment specifically for patients with rare and life-threatening type of immune disease [news release]. Silver Spring, MD: Food and Drug Administration; November 20, 2018. Accessed February 27, 2024. https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm626263.htm

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