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)-neutralizing 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

Gamifant may increase the risk of fatal and serious infections with pathogens including mycobacteria, herpes zoster virus, and histoplasma capsulatum. Do not administer Gamifant in patients with these infections until appropriate treatment has been initiated.

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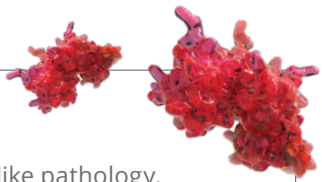
Primary HLH is rapidly progressive and often fatal[2]

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

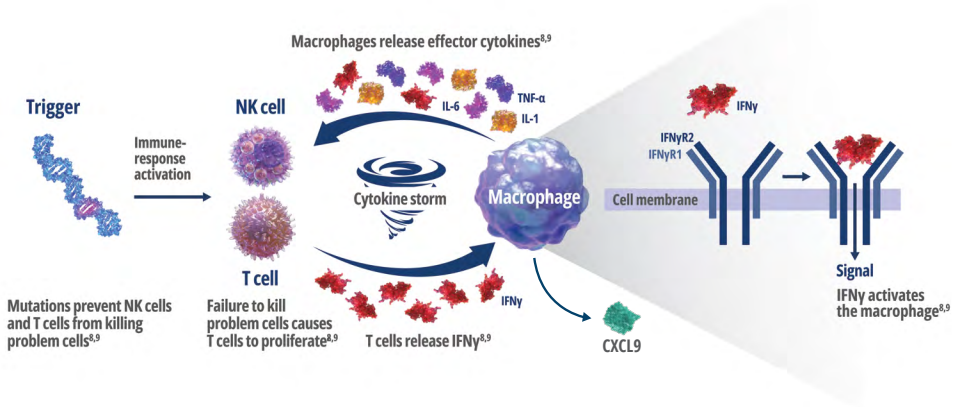
Diagnostic challenges[1,2]

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.

- In primary HLH, genetic mutations prevent perforin pore formation needed for cell lysis[8]
- The failure to kill antigen-presenting cells leads to the proliferation and hyperactivation of T cells[9]
- Activated macrophages release even more T cell and inflammatory cytokines—most notably IFNγ[9]
- Once IFNγ is released, it binds directly to the macrophage's cell receptors[6,8]
- The activated macrophage releases even more cytokines, such as TNF, IL-1, and IL-6. This dangerous cycle leads to the hyperinflammatory symptoms of primary HLH[6,8]

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

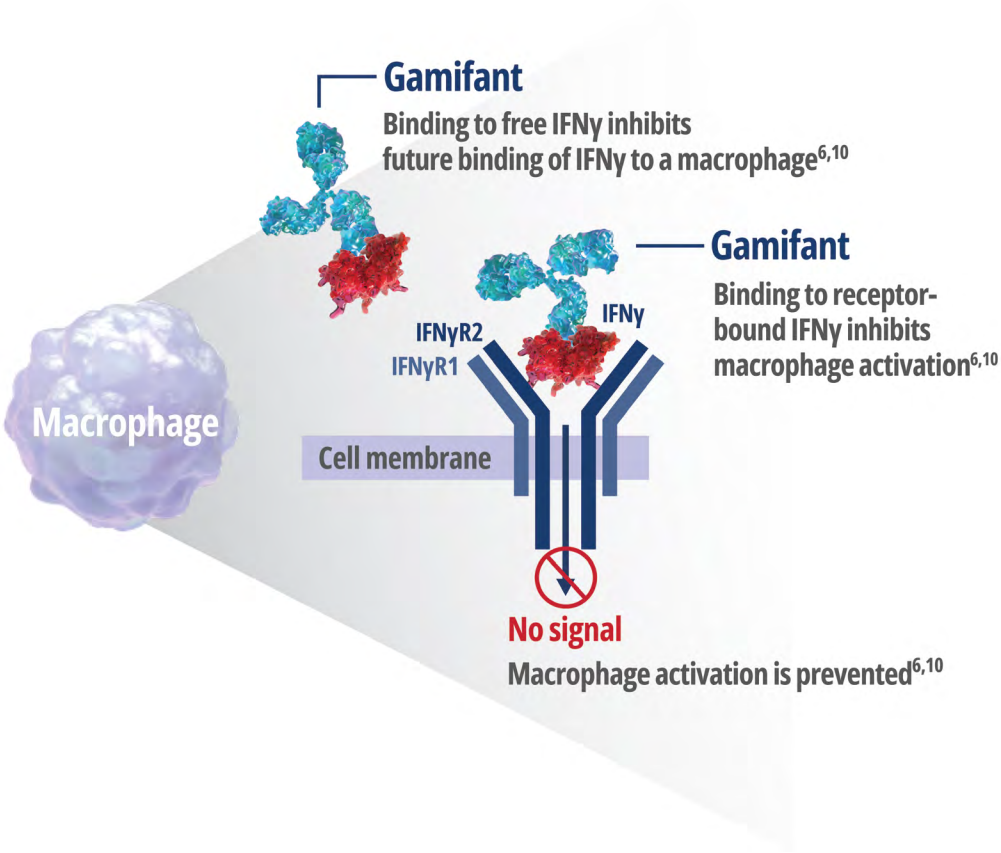
Cincinnati Children's®

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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In patients with primary HLH receiving Gamifant in clinical trials, serious infections such as sepsis, pneumonia, bacteremia, disseminated histoplasmosis, necrotizing fasciitis, viral infections, and perforated appendicitis were observed in 32% of patients.

Evaluate patients for tuberculosis risk factors and test for latent infection prior to initiating Gamifant. Administer tuberculosis prophylaxis to patients at risk for tuberculosis or known to have a positive purified protein derivative (PPD) test result.

Consider prophylaxis for herpes zoster, *Pneumocystis jirovecii*, and fungal infection while receiving Gamifant. Employ surveillance testing during treatment with Gamifant.

Closely monitor patients receiving Gamifant for signs or symptoms of infection, promptly initiate a complete diagnostic workup appropriate for an immunocompromised patient, and initiate appropriate antimicrobial therapy.

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 in patients with primary HLH, 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. Monitor patients for infusion-related reactions, which can be severe. Interrupt the infusion for infusion reactions and institute appropriate medical management before continuing infusion at a slower rate.

Adverse Reactions

Serious adverse reactions were reported in 53% of patients. The most common serious adverse reactions (≥3%) included infections, gastrointestinal hemorrhage, and multiple organ dysfunction. Fatal adverse reactions occurred in 2 (6%) of patients and included septic shock and gastrointestinal hemorrhage.

The most common 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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TO LEARN MORE

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

gamifant.com/phlh

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. 2025. **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 July 28, 2025. https://www.fda.gov/drugs/fda-approves-emapalumab-hemophagocytic-lymphohistiocytosis

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