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Emapalumab-lzsg for Primary Hemophagocytic Lymphohistiocytosis

By: **Cassandra Hacker, Pharm.D.**

Background: Primary hemophagocytic lymphohistiocytosis (HLH) is a rare, but aggressive and life-threatening hyperinflammatory syndrome that usually manifests within the first few months to years of life with the highest incidence in children <3 months.¹⁻³ Characteristic symptoms of HLH include prolonged fevers, cytopenias, coagulopathy, and hepatosplenomegaly. Standard induction therapy for HLH (e.g., dexamethasone, etoposide, cyclosporine A ± intrathecal methotrexate) is used to induce remission prior to a potentially curative hematopoietic stem cell transplantation (HSCT).^{1,4} Agents used off-label for those who are not responsive to or are intolerant to induction therapy have included alemtuzumab, antithymocyte globulin, and anakinra. Although there are data to indicate that these salvage therapies can be effective, there was still a need for a more targeted treatment. Therefore, in November 2018,

the Food and Drug Administration (FDA) approved emapalumab-lzsg (Gamifant®; Sobi) for the treatment of HLH in adult and pediatric patients (newborn and older) with recurrent or progressive disease, or who are refractory or intolerant to conventional HLH therapy.⁵

Mechanism of Action: Interferon gamma (IFN γ) is hypersecreted in HLH which contributes to its hyperinflammatory manifestations.^{5,6} Emapalumab subdues HLH pathogenesis by binding to and neutralizing IFN γ .

Key Clinical Trial: The FDA approval of emapalumab was based on an ongoing open-label pivotal phase II/III trial including pediatric patients (N=34) with suspected or confirmed HLH, the majority (n=27) having failed conventional therapy.² Patients received emapalumab 1 mg/kg intravenously (IV)

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Dupilumab for Eosinophilic or Steroid-Dependent Asthma

By: **Caitlyn Crawford, Pharm.D.**

Background: About 10% of asthmatic patients are thought to have severe eosinophilic asthma with 45% of those affected requiring chronic systemic corticosteroids.^{1,2} The increasing prevalence of this serious often refractory form of asthma has resulted in the Food and Drug Administration (FDA) approving several monoclonal antibody treatments including: mepolizumab, reslizumab, and benralizumab.³⁻⁶ Additionally, in October 2018, the FDA expanded the indication for dupilumab (Dupixent®; Regeneron), to include

add-on maintenance treatment in patients ≥ 12 years of age with moderate-to-severe asthma with an eosinophilic phenotype or with oral corticosteroid-dependent asthma.⁷

Mechanism of Action: Dupilumab targets the alpha subunit of the interleukin (IL)-4 receptor on the surface of eosinophils to inhibit signaling of IL-4 and IL-13.^{7,8} The inhibition of both IL-4 and IL-13 may attenuate symptoms of allergic and eosinophilic asthma.

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every 3 to 4 days administered with dexamethasone 5-10 mg/m²/day for 8 weeks as first-line or second-line therapy after failure or intolerance of conventional induction treatment.^{2,7} Subsequent doses of emapalumab could be increased up to 10 mg/kg based on clinical and laboratory parameters. The primary endpoint of overall response rate (ORR) was defined as normalization or at least 50% improvement from baseline of various symptoms and laboratory abnormalities related to HLH. The ORR in all patients was 64.7% (22/34);p=0.0031 and 63% (17/27);p=0.0134 for the subset failing conventional therapy who received emapalumab as second-line treatment. Complete response was achieved in 20.6% of all patients and 25.9% in treatment-experienced patients. The median time to overall response was 8 days. Emapalumab therapy allowed 64.7% of all patients and 70% of the treatment-experienced patients to proceed to HSCT with a median time to HSCT of 100 days and 83 days, respectively. The authors concluded that emapalumab produced a significant reduction in HLH activity with a tolerable side effect profile allowing patients to proceed to a HSCT.

Safety and Immunogenicity: Some common side effects of emapalumab include infection (56%), hypertension (41%), infusion-related reactions (27%), pyrexia (24%), hypokalemia (15%), and constipation (15%).^{5,6} Prior to initiating therapy, patients should be tested for latent tuberculosis.⁶ Premedication with acetaminophen and diphenhydramine may be used to minimize infusion-related reactions.² It is recommended that prophylactic therapy against herpes zoster, *Pneumocystis jirovecii*, and fungal infections should be provided. Additionally, patients should not receive live or live-attenuated vaccines during therapy and for at least 4 weeks after the last emapalumab dose. The incidence of anti-emapalumab antibody development was 5%, however there has been no evidence of an antibody-associated reduction in efficacy.⁵

Dosing and Administration: The recommended initial dose of emapalumab is 1 mg/kg administered as an IV infusion over 1 hour twice weekly (every 3-4 days).^{5,6} If the patient is not already receiving dexamethasone, it should be given as a dose of 5-10 mg/m² daily, starting the day prior to the first dose of emapalumab. The emapalumab dose can be increased to 3 mg/kg on day 3, and up to 6 mg/kg on day 6 onwards based on certain parameters such as platelet and neutrophil counts, ferritin, worsening of splenomegaly, and coagulopathy; specific dosage adjustments are outlined in the product labeling. Additionally, doses as high as 10 mg/kg/day may be given day 9 and

onwards based on clinical assessment. Emapalumab vials should be stored under refrigeration at 2°C to 8°C (36°F to 46°F) in the original carton, protected from light.^{5,6} Prior to administration the drug should be diluted with 0.9% sodium chloride injection to a concentration range of 0.25 mg/mL to 2.5 mg/mL. The diluted solution needs to be placed in either a gamma irradiated latex-free, polyvinyl chloride (PVC)-free syringe or non-PVC polyolefin infusion bag, depending on the volume needed, and can be stored in the refrigerator for up to 4 hours after preparation. The diluted solution may be allowed to warm to room temperature prior to administration and should be infused through an IV line with a sterile, non-pyrogenic, low-protein binding 0.2 micron inline filter.

Cost and Availability: Emapalumab is available as a preservative-free IV solution in 10 mg/2 mL (NDC 72171-0501-01) and 50 mg/2 mL (NDC 72171-0505-01) vials.^{5,6} The average wholesale price for one 10 mg/2 mL vial is \$4,346 and \$4,453 for one 50 mg/2 mL vial. The cost to complete an 8 week course of therapy for a 6 kg patient at baseline dosing of 1 mg/kg twice a week without up-titration is approximately \$70,000.

Formulary Status: Emapalumab is restricted to Pediatric Hematology/Oncology and Bone Marrow Transplant.

References:

1. Marsh RA, Jordan MB, Talano J, Nichols KE, Kumar A, Naqvi A, Vaiselbuh SR, et al. Salvage therapy for refractory hemophagocytic lymphohistiocytosis: A review of the published experience. *Pediatr Blood Cancer*. 2016 October 27; 64:1-7.
2. Locatelli F, Jordan MB, Allen CE, Cesaro S, Rizzari C, Rao A, Degar B, et al. LBA-6 safety and efficacy of emapalumab in pediatric patients with primary hemophagocytic lymphohistiocytosis. Paper presented at: American Society of Hematology Annual Meeting; 2018 December 3; San Diego, CA.
3. Genetic and Rare Diseases Information Center [Internet] Gaithersburg, MD: National Institutes of Health. Hemophagocytic lymphohistiocytosis; updated 2019 Feb 1. Available from: <https://rarediseases.info.nih.gov/diseases/6589/hemophagocytic-lymphohistiocytosis>. Accessed: February 12, 2019.
4. Jordan MB, Allen CE, Weitzman S, Filipovich AH, McClain KL. How I treat hemophagocytic lymphohistiocytosis. *Blood*. 2011 Oct 13;118(15):4041-52.
5. Gamifant® [package insert]. Stockholm, Sweden: Biovitrum AB; 2018.
6. Lexicomp online [Internet]. Hudson (OH): Wolters Kluwer. c1978-2019 [cited 2019 Jan 22].
7. Gamifant® [product information]. Stockholm, Sweden: Biovitrum AB; 2018.

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Key Clinical Trials: Dupilumab's expanded indication was based on two randomized, phase III, double-blind, placebo-controlled trials. The first trial included patients ≥ 12 years of age with persistent asthma for ≥ 12 months receiving medium-to-high dose inhaled corticosteroids (ICS) plus one or two other asthma controller medicines.⁹ Both eosinophilic and non-eosinophilic asthmatics were evaluated. Participants (N=1902) were randomized in a 2:2:1:1 ratio to receive add-on therapy with dupilumab 200 mg (loading dose, 400 mg, n=631) or 300 mg (loading dose, 600 mg, n=632) subcutaneously every 2 weeks or matching placebo (n=634) for 52 weeks. The co-primary efficacy endpoints were the annualized rate of severe exacerbation events and absolute change from baseline in forced expiratory volume in the first second (FEV₁) at week 12. The annualized rate of severe asthma exacerbations was significantly lower among patients who received either dupilumab 200 mg or dupilumab 300 mg every 2 weeks compared to placebo (p<0.001 for both comparisons). At week 12, the FEV₁ change from baseline before bronchodilator use was significantly greater in patients who received either dupilumab 200 mg or 300 mg regimens than those who received placebo (p<0.001 for both comparisons). Greater benefit was observed in patients with higher baseline eosinophil levels. The second trial was a 24-week study with inclusion criteria similar to the first trial except patients were required to have glucocorticoid-dependent asthma.² Patients (N=210) were randomized in a 1:1 ratio to receive dupilumab 300 mg (loading dose, 600 mg, n=103) subcutaneously every 2 weeks or placebo (n=107). The primary endpoint was the percentage reduction of oral corticosteroid (OCS) dose at week 24 while maintaining asthma control. The least-square mean (\pm SE) percentage change in OCS dose from baseline to week 24 while asthma control was maintained was $-70.1 \pm 4.9\%$ in the dupilumab group compared with $-41.9 \pm 4.6\%$ in the placebo group (p<0.001). At week 24, there was also a significant difference in the number of patients who discontinued use of OCS, with 48% in the dupilumab group versus 25% in the placebo group (p=0.002). In addition to significant reductions OCS use, patients who received dupilumab treatment had a 59% lower rate of severe asthma exacerbations.

Safety: Hypersensitivity reactions were reported in <1% of patients.^{7,8} Common side effects included injection-site pain (14-18%), conjunctivitis (10%), oropharyngeal pain (2%), and eosinophilia (2%). Patients should be monitored for infection, new onset or worsening ocular symptoms, and hypersensitivity.

Dosing and Administration: The recommended dosage of dupilumab as add-on maintenance therapy for patients ≥ 12 years of age with moderate-to-severe eosinophilic or oral corticosteroid-dependent asthma is either 400 mg (administered as two 200 mg injections) as an initial dose followed by 200 mg injection every other week or 600 mg (administered as two 300 mg injections) as an initial dose followed by 300 mg every other week.^{7,8} For patients requiring concomitant oral corticosteroids or with co-morbid moderate-to-severe atopic dermatitis for which dupilumab is indicated, the initial dose is 600 mg followed by 300 mg every other week. Injections should be administered subcutaneously into the upper arm, thigh, or abdomen. The first dose must be administered by a healthcare professional, but subsequent doses may be self-administered. Dupilumab pre-filled syringes should be refrigerated in their original carton, but may be kept at room temperature for up to 14 days.

Availability and Cost: Dupilumab is available as both 200 mg/1.14 mL and 300 mg/2 mL pre-filled syringes.⁷ The product has a suggested wholesale price (SWP) of \$1,812 for either the 200 mg or 300 mg pre-filled syringe and therefore, the cost of 12 months of therapy would be approximately \$45,000.⁸

Formulary Status: The restriction for dupilumab was expanded to include Staff Physicians from the Departments of Allergy/Immunology and Pulmonary/Critical Care Medicine for use in the outpatient setting.

References:

1. American Partnership for Eosinophilic Disorders [Internet] USA: American Partnership for Eosinophilic Disorders. Eosinophilic Asthma; 2018. Available from: <https://apfed.org/about-ead/eosinophilic-asthma/>. Accessed February 1, 2019.
2. Rabe KF, Nair P, Brusselle G, Maspero JF, Castro M, Sher L, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. *N Engl J Med.* 2018 Jun 28;378(26):2475-85.
3. Fajt ML, Wenzel SE. Asthma phenotypes and the use of biologic medications in asthma and allergic disease: the next steps toward personalized care. *J Allergy Clin Immunol.* 2015;135(2):299-309.
4. Nucala® [package insert]. Philadelphia, PA: GlaxoSmithKline; Dec 2017.
5. Cinquair® [package insert]. Frazer, PA: Teva Respiratory; June 2016.
6. Fasenra® [package insert]. Wilmington, DE: AstraZeneca; Nov 2017.
7. Dupixent® [package insert]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc; Oct 2018.
8. Lexicomp Online, Lexi-Drugs, Hudson, Ohio: Lexi-Comp, Inc; 2019; February 1, 2019.
9. Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med.* 2018; 28;378(26):2486-96.