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Weathering the Cytokine Storm: Anakinra Use in HLH

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Disclosures

- Kelley R. Norris, Pharm.D., BCPS, BCPPS
  - I have no financial disclosures regarding the content of this presentation.
  - I will be discussing off label use of anakinra.
- Margaret O. Poisson, Pharm.D., BCPPS
  - I have no financial disclosures regarding the content of this presentation.
  - I will be discussing off label use of anakinra.

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Objectives

- Identify the role of anakinra in HLH
- Discuss clinical outcomes of anakinra use in secondary HLH
- Describe dosing strategies of anakinra in the pediatric population

HLH: Hemophagocytic lymphohistiocytosis

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HLH

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Cell Lines

- Macrophages
  - Antigen presenting cells (APC) derived from monocytes
  - Present foreign antigen to lymphocytes
- Natural Killer (NK) Cells
  - Eliminate damaged, stressed or infected host cells (macrophages)
- Cytotoxic T lymphocytes (CTL)
  - Lyse autologous cells presenting foreign antigen

Risma K, et al. Curr Opin Pediatr 2012.24(1):9-15
Filipovich A, et al. Biol Blood Marrow Transplant 2012. 16(1 Supp):S82-9

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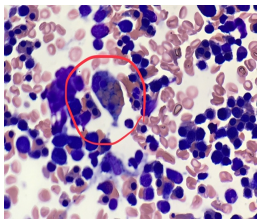
Hemophagocytosis

- Phagocytosis of host cells (red blood cells, leukocytes, and platelets) by macrophages
- Occurs after over-activation of macrophages due to dysregulated immune response



Risma K, et al. Curr Opin Pediatr 2012.24(1):9-15
Filipovich A, et al. Biol Blood Marrow Transplant 2012. 16(1 Supp):S82-9

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HLH

- Aggressive and life threatening syndrome of excessive immune activation
- Excessive cytokine release leading to a cytokine storm
  - IL-2 (CD25), IL-6, IL-10, IL-12, IL-18, TNFα, IFNγ
- Systemic inflammatory response

Risma K, et al. Curr Opin Pediatr 2012.24(1):9-15
Filipovich A, et al. Biol Blood Marrow Transplant 2012. 16(1 Supp):S82-9

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Primary HLH

- Inherited
  - Known as familial hemophagocytic lymphohistiocytosis (FHL)
  - Due to an autosomal recessive gene mutation
    - Occurs at one of the FHL loci or in a gene involved in an immunodeficiency syndrome

Larroche C. Joint Bone Spine 2012;79:356

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Secondary HLH

- Acquired
  - Generally caused by a trigger (viral illness, autoimmune disease, lymphoma)
  - May have some underlying genetic cause
  - Macrophage activation syndrome (MAS)
    - **HLH in the setting of a rheumatologic disorder**
    - Occurs primarily in patients with juvenile idiopathic arthritis (JIA)
  - MODS (multiorgan dysfunction syndrome)
    - Progressive organ dysfunction in acutely ill patient
    - Can have overlap in diagnosis with HLH

Fukaya S, et al. Rheumatology 2008;47(11):1686-91
Davi S, et al. Arthritis Rheumatology 2014;66(10)2871-80
Nahum E et al. Pediatr Crit Care Med 2000;1(1):51

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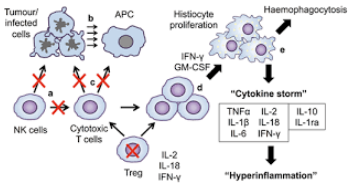
Pathophysiology of HLH



Carter S, et al. Rheumatology 2018;58(1):5-17

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HLH Diagnostic Criteria

- Fever
- Splenomegaly
- Cytopenias affecting ≥ 2 lineages
  - Hemoglobin < 9g/dL; < 4 weeks: Hemoglobin < 10g/dL
  - Platelets < 100 x 10^3 per µL
  - Neutrophil < 1000 x 10^3 per µL
- Hypertriglyceridemia (fasting > 265mg/dL)
- Hyperfibrinogemia (< 150mg/dL)
- Hemophagocytosis (bone marrow, cerebral spinal fluid)
- Ferritin > 500ng/mL
- Low/absent NK cell activity
- IL-2 (CD25) > 2400 units/ml

Henter JI, te al. Pediatr Blood Cancer 2007;48(2)

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Pathophysiology of Signs & Symptoms

- Fever: overproduction of IL-1
- Pancytopenia: TNFα and IFNγ
- High ferritin: Secreted by activated macrophages
- Low fibrinogen: plasminogen activator secreted by macrophages leads to fibrinogen consumption
- Elevated IL-1: Activated lymphocytes secrete soluble CD25 (sCD25) which infiltrates the liver and central nervous system

Filipovich A, et al. Biol Blood Marrow Transplant 2012. 16(1 Supp):S82-9

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MANAGEMENT OF HLH

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Markers for Monitoring

- Clinical Response
  - Physical exam
  - Ferritin
  - Complete blood count with differential
  - Coagulation
  - Liver function
  - Cerebral spinal fluid in patient with abnormalities
- Disease Specific Markers
  - Ferritin
  - NK cell function
  - IL-6, IL-18
  - sCD25 (soluble IL-2 receptor)/sCD163 (soluble hemoglobin-haptoglobin scavenger receptor)

Henter JI, et al. Pediatr Blood Cancer 2007;48(2)
Lin TF, et al. Pediatr Blood Cancer 2011;56(1):154
Jordan M. Hematologist 2018;15(2)

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HLH Treatment Protocols

- May be difficult to distinguish primary from secondary HLH
- Treatment protocols designed primarily for primary HLH
  - Initial therapy aimed to achieve remission prior to hematopoietic stem cell transplant (HSCT)
- Due to high associated mortality, 94-HLH protocol included patients with secondary HLH
- HLH-2004 protocol designed for the patients with HLH, with or without evidence of familial or genetic disease, regardless of suspected or documented viral infections.

Henter JI, et al. Blood 2002; 100(7)
Henter JI, et al. Pediatr Blood Cancer 2007;48(2)

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HLH Treatment Protocol Comparisons

HLH-94

- Initial: 8 weeks of Etoposide and dexamethasone
- Continuation (Week 9 onward): Dexamethasone, Etoposide, oral cyclosporine for children with known familial disease or persistent non-familial disease
- Continuation recommended to keep stable prior to HSCT
- Intrathecal (IT) Methotrexate (MTX) (maximum 4 doses) : For progressive neurologic symptoms or abnormal CSF non-improving

HLH-2004

- Initial: 8 weeks of Dexamethasone, Etoposide, **Cyclosporine**
- **Addition of hydrocortisone to MTX**
- Reactivation (at any point): Intensification of therapy is recommended followed by continuation therapy until HSCT
- No salvage protocol. Recommend discussion with center. Alternative mentioned (steroids, CSA, ATG) but ATG may not be effective in non-responders
- Therapy is continued indefinitely until complete resolution of disease

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Henter JI, et al. Blood 2002; 100(7)
Henter JI, et al. Pediatr Blood Cancer 2007;48(2)

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Principles of Treatment

Symptomatology	Medication Therapy
Suppression of inflammation	Corticosteroids IV Immunoglobulins (IVIG) Cyclosporine Anti-cytokine agents (anakinra, emapalumab, tocilizumab, ruxolitinib)
Elimination of activated immune cells (CTLs and APC)	Corticosteroids Etoposide T-cell antibodies (anti-thymocyte globulin (ATG), alemtuzumab)
Elimination of trigger	Anti-infectious therapy
Supportive therapy	Anti-fungals, plasma and blood products
Defective immune system	Hematopoietic stem cell transplant

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Jordan M. Hematologist 2018;15(2)
Bergsten E et al. Blood 2017;130(25):2728

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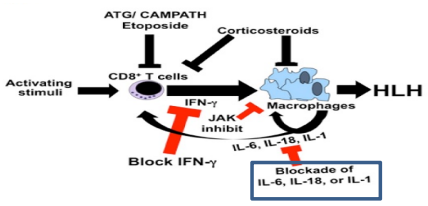
Targeted Therapies



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Jordan M. Hematologist 2018;15(2)

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Anakinra

- Mechanism of action
  - Interleukin-1 receptor antagonist
- Bioavailability: 95% via subcutaneous (SC) route
- Time to peak: 3-7 hours
- Distribution: joint, kidney, bladder, spleen, liver and bowel
- Excretion: primarily by kidney
  - Requires dose adjustment in renal dysfunction
  - Dialyzed <2.5% in hemodialysis and peritoneal dialysis
- Half-life: 4-6 hours

Kineret [package insert]. Stockholm, Sweden: Swedish Orphan Biovitrum AB; 2018
Anakinra. Lexi-Drugs. Lexicomp. Wolters Kluewer Health, Inc. Riverwoods, IL. Available at http://online.lexi.com. Accessed February 2019

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Anakinra

- FDA approved for
  - Rheumatoid arthritis in patients 18 years of age or older who have failed 1 or more disease modifying anti-rheumatic drugs
  - Cryopyrin-associated periodic syndromes (CAPS)
    - Treatment of neonatal-onset multisystem inflammatory disease
- Supplied As: 100 mg/0.67 mL solution prefilled syringe
  - Graduated syringe allows for doses between 20 and 100 mg
- AWP Price: 100 mg/0.67 mL (per 0.67 mL): $176.48

Kineret [package insert]. Stockholm, Sweden: Swedish Orphan Biovitrum AB; 2018
Anakinra. Lexi-Drugs. Lexicomp. Wolters Kluewer Health, Inc. Riverwoods, IL. Available at http://online.lexi.com. Accessed February 2019

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Summary of Literature

Study/Population	Anankinra Dosing	Endpoints	Results
Miettunen 2011 Case series (n = 12) 0.5 – 17 Years Old Rheumatic Disease-Related MAS episodes	2mg/kg/day SC (max 100mg) in addition with high-dose corticosteroids, IVIG, and cyclosporine	Ferritin CRP	Remission of MAS within a median of 13 days (2-19) Ferritin and CRP had strong correlation with resolution
Bruck 2011 Case series (n = 2) 8 and 12 Year Old Diagnosed with JIA, MAS, and HLH	2 mg/kg/day SC plus prednisolone/indomethacin or dexamethasone	Ferritin CRP D-dimers Transaminases Neutrophil count	All laboratory values normalized within • 20 days (patient 1) • 14 days (patient 2) Initial clinical and laboratory improvement not exclusive to anakinra

CRP: C-reactive Protein

Miettunen P, et al. Rheumatology 2011;50:419-20
Bruck N, et al. J Clin Rheumatol 2011;17:23-7

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Summary of Literature

Study/Population	Anankinra Dosing	Endpoints	Results
Rajasekaran 2014 Case Series (n = 8) 8-21 Years Old Secondary HLH	Not reported for each patient. Per prescribing rheumatologist In addition to IVIG (n = 5) and high-dose corticosteroid (n = 6) Anakinra dose adjusted based on clinical response	CRP Ferritin Fibrinogen Creatinine LDH ANC Platelets	All markers showed decline 1 week after Anakinra CRP ↓ 67.1% and fibrinogen ↓ 42% (p = 0.03) Mean serum ferritin ↓ 63.8% (p = 0.3) ANC ↓ 30.2% (p = 0.38) Platelets ↓ 29.3 % (p >0.99)
Sonmez 2017 Systematic Review Pediatric (n = 15; 13 MAS; 2 AIDS) sJIA or AIDS ± MAS episode	2mg/kg/day (1 – 6.7mg/kg/day) with pulse methylprednisolone ± Cyclosporine A; ±IVIG Dose increased if no response to ferritin and thrombocyte counts in 12 hours	Resolution of fever Normalization of laboratory parameters Cessation time of steroid Remission Recurrent MAS	Clinical symptom resolution [median 2 (1-4) days] Normalization of laboratory findings [median 6 (4-9) days] Steroid stopped [median 10 (4-13) weeks]

AIDS: Acquired Immunodeficiency Syndrome
LDH: Lactate Dehydrogenase
ANC: Absolute Neutrophil Count

Rajasekaran S,et al. Pediatr Crit Care Med 2014;15(5):401-8
Sonmez H, et al. Clinical Rheumatology 2018;37:3329-35

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Duration

- Duration of anakinra varied greatly in published studies
- Serologic marker decline proposed as determining factor for tapering anakinra
- Majority of patients were continued on anakinra indefinitely

Miettunen P, et al. Rheumatology 2011;50:419-20
Bruck N, et al. J Clin Rheumatol 2011;17:23-7
Rajasekaran S,et al. Pediatr Crit Care Med 2014;15(5):401-8
Sonmez H, et al. Clinical Rheumatology 2018;37:3329-35

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Is It Worth the Squeeze

- Mortality rates for HLH (primary and secondary) are still high despite surrogate marker improvement
  - Despite 63.8% decline in ferritin, mortality was still 12%
  - Despite optimal treatment, 50% of patients die with HLH.

Rajasekaren S, et al. Pediatr Crit Care Med 2014;15
Ysabella M, et al. Pediatric Annals 2017;46(8)

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More Is Not Always Better

- Highly variable dosing
  - 1mg/kg/day – 12mg/kg/day
  - Continuous infusion
- Higher dosing requirements have been proposed in children
- More frequent dosing than once daily has also been proposed to achieve IL-1 inhibition
  - Short half life
- No data evaluating increased doses/frequency and clinical outcomes
- No mortality benefit reported in severe sepsis

Opal SM et al, Crit Care Med 1997: 25(7)
Rajasekaran S,et al. Pediatr Crit Care Med 2014;15(5):401-8
Nigrovic P, et al. Arthritis and Rheumatism 2011;63(2)
Peng,T, et al. J Rheum Dis Treat 2015;1(2)

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Routes of Administration

- Approved for subcutaneous administration
  - Recommended route of administration
- Intravenous administration has been published widely
  - IV bolus (as undiluted drug)
  - IV continuous infusion
- Frequency of adverse events between SC and IV shown to be no different

Fisher CG et al, JAMA 1994: 271(23)
Fisher CG et al, Crit Care Med 1994: 22(1)
Opal SM et al, Crit Care Med 1997: 25(7)
Granowitz EV et al, Cytokine 1992;4(5)
Yang BB, et al. Clin Pharmacol Ther 2003;74(1)
Emsley HC, et al. J Neurol Neurosurg Psychiatry 2005;76(10)
Singh N, et al. J Neuroinflammation 2014;11(1)
Galea J, et al. J Cereb Blood Flow Metab 2011;31(2)

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SAFETY

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Limited Toxicity

- Anakinra has no significant reported safety issues
- Events that occurred at a frequency ≥5%
  - Pain at the injection site (most common in studies)
  - Headache
  - Skin rash
  - Nausea/Vomiting
  - Increased infections

Peng T, et al. J Rheum Dis Treat 2015;1(2) Shakoory B, et al. Crit Care Med 2016;44(2)
Bruck N, et al. J Clin Rheumatol 2011;17
Kineret [package insert]. Stockholm, Sweden: Swedish Orphan Biovitrum AB; 2018
Anakinra. Lexi-Drugs. Lexicomp. Wolters Kluewer Health, Inc. Riverwoods, IL. Available at http://online.lexi.com. Accessed February 12, 2018

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CLINICAL SCENARIO

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Neonatal Case Utilizing Anakinra

- 2 week old male (term) with no PMH presents to the PICU with fever and evaluation for pneumonia
  - Admitted 5 days prior for fever secondary to adenovirus
  - Persistently febrile since discharge with decreased oral intake
  - Found to have disseminated (+ liver involvement) adenovirus and started on cidofovir and probenecid

PMH: Past Medical History
PICU: Pediatric Intensive Care Unit

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Neonatal Case Utilizing Anakinra

- 2 week old male (term) with no PMH presents to the PICU with fever and evaluation for pneumonia
  - Ferritin level obtained 5 days after admission >1500
  - HLH diagnosed by bone marrow biopsy
    - CNS involvement noted

CNS: Central Nervous System

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Therapeutic Management

- Due to worsening hypoxia, VV ECMO was initiated
- Started dexamethasone, etoposide, and anakinra for HLH
- 3 days after ECMO cannulation, CVVH initiated due to diminished urinary output and rising creatinine
  - Limitations with anakinra
    - Dose measurability
    - Renal dose adjustment
    - Dosing in ECMO

VV ECMO: Veno-Venous Extracorporeal Membrane Oxygentation
CVVH: Continuous Veno-Venous Hemofiltration

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Suggested Anakinra Approach (Per Kelley and Margaret)

- Data for anakinra exists only in secondary HLH
  - Potential role in both primary and secondary HLH based on pathophysiology
- Recommend starting at the lower end of dosing range SC given once daily
  - Aggressiveness of dosing varies based on primary versus secondary HLH indication
    - Increase dose and frequency based on daily ferritin response

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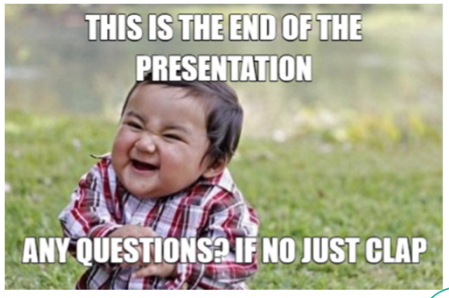

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