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Review Article

Hemophagocytic Lymphohistiocytosis: Its Biochemical Basis and Clinical Implications

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening syndrome characterized by excessive cytokine activation. Its treatment remains extremely limited, with high mortality. Recent research into its pathogenesis has revealed the major role of cytokines, such as interferon-gamma (IFN-γ), tumor necrosis factor-alpha, interleukin-1 (IL-1), IL-6, and IL-18. These cytokines may also help identify HLH in the early stage or predict HLH in high-risk patients in the future. Both animal and human research provide evidence of the role of biochemical mediators in HLH. In addition, the interplay between cytokines and cells in the pathogenesis of HLH has opened up new targeted therapeutics. These treatment alternatives are being tried for the primary and secondary forms of HLH, with promising results. Emapalumab, an anti-IFN-γ monoclonal antibody, has been widely studied in HLH with favorable results. Anti-IL-1 receptor antibody (anakinra), anti-IL-18 neutralizing molecule (tadekinig-α), and anti-CD52 monoclonal antibody (alemtuzumab) are among the newer drugs in the pipeline for the treatment of HLH. Small molecule inhibition beyond receptor activation in cells has previously had immense success in treating spondylarthritis and leukemia. Ruxolitinib, a Janus kinase inhibitor, also demonstrated positive outcomes in HLH treatment. With these emerging treatment options, the future outlook for HLH is moving toward a promising new horizon.

Keywords: Hemophagocytic, Lymphohistiocytosis, Inflammation, Cytokines, Interferons, Interleukins

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Background

Hemophagocytic lymphohistiocytosis (HLH) is a syndrome of immune activation (1) that may occur in people with a genetic predisposition or de novo. The aggressive immune activation and tissue destruction observed in HLH are life-threatening (1). Prompt identification and early initiation of treatment can save lives. An understanding of HLH pathophysiology is still evolving. Excess immune activation and tissue destruction in HLH are well known. The biochemical basis of HLH has recently been explored, leading to the discovery of many important cytokines and chemokines in the pathophysiology of HLH. These molecules attract new possible therapeutic targets in HLH treatment. This review focuses on recent advances in the biochemical basis of HLH and its clinical implications.

The Histiocyte Society described the first standard definition of HLH in 1994 as part of the HLH-94 clinical trial (2). This definition was revised later in 2004 for the HLH-2004 trial (3). Both HLH-94 and HLH-2004 criteria and treatment protocols are based on paediatric trials and thus lack validation in the adult population (2). Recently, the American Society of Hematology published recommendations for HLH diagnosis and management in adults (4). Historically, HLH has been divided into primary or familial and secondary subtypes. The primary HLH is inherited and presents in the first year of life. It is lethal without treatment. On the other hand, the secondary HLH presents later in life, triggered by various infections, autoimmune diseases, or malignancies. Recent data indicate that even secondary HLH may have genetic risks, thus blurring this rigid division. The North American Consortium for Histiocytosis recommends classification based on the etiology, which may be more practical and has greater implications for management (5). This group has an interesting viewpoint on the classification of HLH into HLH syndrome, HLH disease, and HLH disease-mimics. The HLH syndrome includes all patients meeting consensus diagnostic criteria. When the distinctive immune regulation remains the core problem, and they are likely to benefit from immunosuppression, it is called 'HLH disease'. Conditions that may have the

HLH pattern, but require entirely different treatment, are termed 'HLH disease-mimics'. This classification removes several ambiguities noted in the dichotomous classification into primary and secondary HLH. It helps in the cautious exclusion of conditions that may be harmed by immunosuppression (e.g., infections and malignancy). It further brings to mind the possibility of mutations as a risk factor in several environmentally triggered HLH, which were previously lumped into the umbrella of secondary HLH (5).

International studies quote an incidence of 1 in 50,000 live births for familial HLH (6,7). Data on the incidence and prevalence of HLH obtained from India are severely lacking. A retrospective analysis from an intensive care unit setting in a tertiary care hospital reported a prevalence of 1.04% (8). Another retrospective analysis demonstrated that the characteristics of molecularly diagnosed familial HLH across 20 centres in India had 101 patients over 10 years (1). The cost of genetic analysis limits diagnosis, and HLH may be underdiagnosed in even tertiary care settings in India.

HLH can have variable manifestations, and individual symptoms can be observed in various other diseases, making the diagnosis challenging. Fever, the deterioration of the general state, splenomegaly, hepatomegaly, lymphadenopathy, and bleeding are among the most common manifestations of HLH (9). Other symptoms include hyperferritinemia, hypertriglyceridemia, hypofibrinogenemia, pancytopenia, hemophagocytosis in the bone marrow, and elevated soluble CD25 (sCD25, where CD is the cluster of differentiation) levels. The HLH-score has been validated in predicting an individual's risk of having reactive hemophagocytic syndrome (10). The HScore is a validated diagnostic tool designed to estimate the probability of HLH in patients with hyperinflammatory symptoms. It incorporates nine clinical and laboratory parameters, including fever, organomegaly (splenomegaly or hepatomegaly), cytopenias (affecting two or more lineages), hypertriglyceridemia, hypofibrinogenemia, hyperferritinemia, elevated aspartate aminotransferase, hemophagocytosis on bone marrow examination, and elevated sCD25 levels. Each parameter is assigned a weighted score, and the cumulative total helps clinicians assess HLH likelihood. In the original study, the probability of having hemophagocytic syndrome ranged from < 1% with an HScore of ≤ 90 to > 99% with an HScore of ≥ 250 (10).

HLH is diagnosed based on the patient's history, clinical judgement, and the HLH-2004 diagnostic criteria (3, 11).

Immunopathology of Hemophagocytic Lymphohistiocytosis

HLH is a life-threatening hyperinflammatory syndrome driven by dysregulated immune activation, resulting in a cytokine storm that causes widespread tissue damage and multi-organ failure. This article primarily focuses on the biochemical mediators of HLH, particularly the role of cytokines in its pathogenesis; however, first, it provides a concise overview of the immunopathological mechanisms to contextualise these mediators. This section elucidates the roles of key immune cells, the hallmark process of hemophagocytosis, and the diverse triggers contributing to HLH pathogenesis, thereby integrating insights from recent studies to provide a comprehensive understanding.

Key Cellular Players

The immunopathology of HLH is characterized by the uncontrolled activation of macrophages, natural killer (NK) cells, and cytotoxic T lymphocytes (CTLs), which all trigger a hyperinflammatory state.

Macrophages

Hyperactivated macrophages are central to HLH, presenting antigens to lymphocytes and secreting excessive pro-inflammatory cytokines, such as interleukin-1 (IL-1), IL-6, and tumor necrosis factor-alpha (TNF-α), which amplify inflammation and cause severe tissue damage (12–14). This cytokine storm is a hallmark of HLH, leading to systemic inflammation and organ dysfunction. Recent studies have highlighted that macrophages also produce autoantibodies and immune complexes, further exacerbating immune activation.

Natural Killer Cells and Cytotoxic T Lymphocytes

NK cells and CD8 + CTLs normally eliminate infected or malignant cells via perforin-mediated and granzyme-mediated cytotoxicity. CTLs act through major histocompatibility complex (MHC) class I-restricted mechanisms, while NK cells operate independently of MHC restrictions. In HLH, these cells exhibit impaired cytotoxic function, thereby failing to clear hyperactivated macrophages or infected cells, a process termed defective "fratricidal killing" (12-15). This dysfunction leads to sustained immune activation, perpetuating the cytokine storm. Recent research confirms that defective perforin secretion, often due to genetic mutations in primary HLH, disrupts the formation of lytic pores in target cells, exacerbating inflammation.

Hemophagocytosis

Hemophagocytosis, a hallmark of HLH, involves aberrantly activated macrophages engulfing red blood cells, white blood cells, and platelets, observable in bone marrow, spleen, or lymphoid tissues (2,16). This process reflects excessive macrophage activation but is neither specific nor diagnostic for HLH, as it can occur in other inflammatory conditions, such as sepsis or malignancy (2,16). Microscopic findings (e.g., macrophages phagocytosing erythrocytes or erythroblasts in bone marrow) underscore this feature, but its absence in early biopsies does not rule out HLH. Elevated levels of sCD25 and hyperferritinemia often correlate with hemophagocytosis, reflecting the underlying immune dysregulation.

Triggers of Hemophagocytic Lymphohistiocytosis

HLH is classified into primary (familial) and secondary (acquired) types, each with distinct triggers that precipitate acute episodes.

Primary Hemophagocytic Lymphohistiocytosis

Genetic mutations, such as those in the perforin gene (*PRF1*) or genes like *Unc-13 Homolog D*, *Syntaxin 11*, and Syntaxin Binding Protein 2, impair cytotoxic function, thereby predisposing individuals to primary HLH (4,14). These mutations disrupt granule-dependent cytotoxicity, leading to uncontrolled immune activation. Several syndromes, such as Chédiak-Higashi, Griscelli type II, and Hermansky-Pudlak type II, which involve defective granule secretion, also predispose to HLH, often presenting with partial albinism and platelet dysfunction.

Secondary Hemophagocytic Lymphohistiocytosis

This type of HLH is triggered by infections, malignancies, autoimmune diseases, or medications. Epstein-Barr virus (EBV) is the most common infectious trigger, initiating an exaggerated immune response (4,16). Other triggers include viral (e.g., cytomegalovirus and human immunodeficiency virus), bacterial (e.g., Rickettsia), fungal, and protozoal (e.g., leishmaniasis) infections. Malignancies, particularly non-Hodgkin lymphomas (T-cell and B-cell), are frequent triggers in adults, with 91.6% of lymphoma-associated HLH cases presenting in advanced stages (III/IV). Autoimmune conditions, such as systemic lupus erythematosus or vasculitis, can induce macrophage activation syndrome (MAS), a form of secondary HLH. Recent reports also link immune checkpoint inhibitors and antibiotics (e.g., trimethoprim/sulfamethoxazole) to HLH, likely via drug hypersensitivity reactions (17).

Common Mechanisms

Both primary and secondary types of HLH share a common pathway of immune dysregulation, where triggers amplify defective cytotoxic function, leading to persistent T-cell and macrophage activation. This results in elevated cytokine levels, such as interferon-gamma (IFN-γ) and IL-18, causing systemic inflammation, often requiring prompt intervention to prevent multi-organ failure.

This enhanced understanding of HLH immunopathology underscores the interplay of cellular dysfunction, hemophagocytosis, and diverse triggers, providing a foundation for exploring targeted diagnostics and therapies.

Biochemical Mediators in Hemophagocytic Lymphohistiocytosis

The cytokine storm in HLH is its most dreaded consequence. The cytokine storm has recently been increasingly recognised as a major player in tissue destruction. Recent experience with the coronavirus disease 2019 pandemic has reminded us that an exaggerated immune response can lead to lethality, regardless of the pathogen (18).

In HLH, the persistent activation of macrophages, NK cells, and CTLs leads to excess cytokine production. These cytokines can either promote or suppress the pathology of HLH. Cytokines (e.g., IFN-γ and TNF-α), ILs (e.g., 6, 10, and 12), and sCD25 are elevated (19). Biologically active, free IL-18 is also found to increase in secondary HLH (20).

Some important biochemical mediators of the cytokine storm in HLH will be further discussed in the following sections. Figure 1 depicts the interplay of cytokines in HLH and the involved cell types.

Interferon-Gamma

IFN-γ plays a pivotal role in HLH pathology, as it is a proinflammatory cytokine involved in immune cell activation and antigen presentation enhancement (21,22). In addition, it is particularly vital in progressing certain hematologic conditions, including HLH and aplastic anemia. Produced primarily by NK cells during the innate immune response and by CD4 + T-helper 1 and CD8 + CTL cells in adaptive immunity, IFN-γ has been identified as critical in HLH onset (21). Several studies have underscored its essential contribution to HLH, with human and animal studies reporting elevated IFN-γ and/or chemokine-C-X-C motif ligand 9 levels in HLH cases (5,23,24). Diagnostic potential lies in measuring IFN-γ in blood, such as through the QuantiFERON- tuberculosis assay (25). Moreover, IFN-γ is necessary for HLH-like symptoms in animal models (25). The findings indicate that IFN-γ overproduction exacerbates hematologic symptoms, while IL-2 overconsumption contributes to immune-related signs (26). Likewise, human studies report that IFN-γ levels are disproportionately high in HLH patients, demonstrating marked reductions post-treatment with certain drugs (27,28). These insights support the potential use of IFN-γ inhibitors as novel therapeutic approaches for HLH.

Interleukin-1 Beta

The cytokine IL-1β is predominantly produced by activated macrophages. It stimulates white blood cells and endothelial cells and promotes other inflammatory cytokines, such as IL-6 (12). In addition, IL-1β is stored in its inactive proIL-1β form within the cell cytosol, where its activation is closely associated with the nucleotide-binding and oligomerization domain (NOD)-like receptor family pyrin domain containing 3 (NLRP3) inflammasome and caspase-1 enzyme (29). Caspase-1 activation relies on various inflammasomes within gene families, including NOD-NLRs and tripartite motif proteins (29,30). Through external adenosine triphosphate stimulation via the purinergic receptor P2X (P2X7) receptor, procaspase-1 engages the NLRP3 inflammasome, allowing for IL-1β activation and subsequent release from the cell (29,30). IL-1β is strongly associated with systemic onset Juvenile idiopathic arthritis (soJIA), an important condition linked to HLH (31).

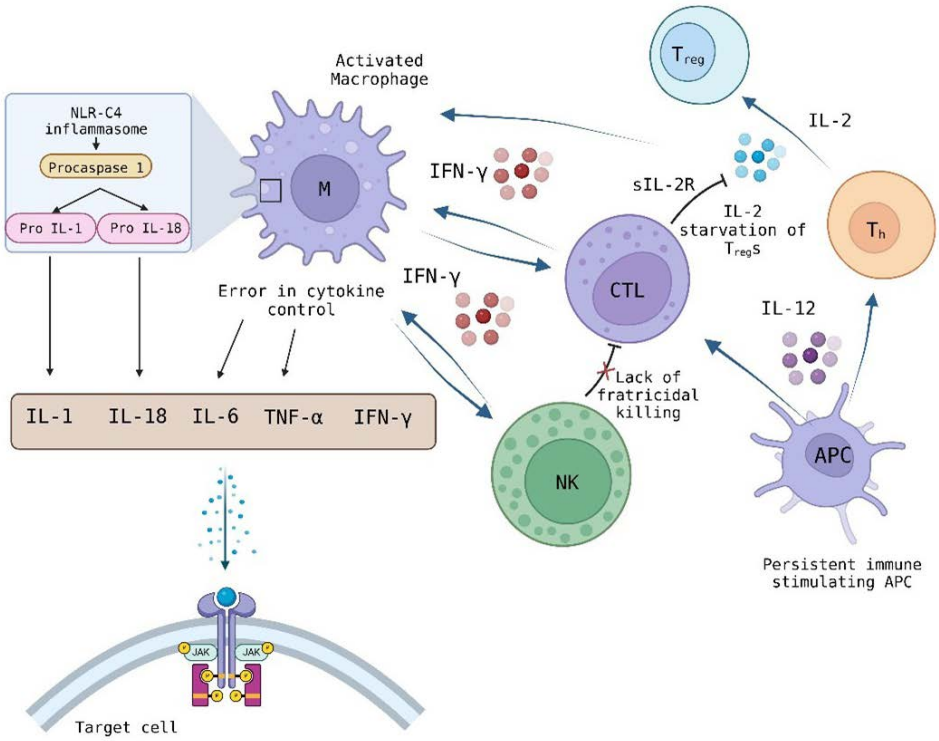

Figure 1. The Interplay of Cytokines in Hemophagocytic Lymphohistiocytosis. Source. Created in BioRender. Punjadath, Sryla (2024). https://BioRender.com/t22h322

Interleukin-6

Produced by macrophages, IL-6 is a multifunctional cytokine released during early inflammation, alongside TNF-α and IL-1β (32). When IL-6 binds to its receptor IL-6R, it initiates a signalling cascade through gp130, activating the Janus kinase-signal transducer and activator of transcription 3 (JAK-STAT3) pathway and the Janus kinase-Src homology 2 domain containing protein tyrosine phosphatase 2-mitogen-activated protein kinase pathway (32). This process leads to STAT3 phosphorylation (33). Once in the nucleus, STAT3 regulates genes that drive inflammation, cell survival, proliferation, immune responses, and feedback inhibition (34). STAT3-driven IL-6 signalling also stimulates the suppressor of cytokine signalling 1 and cytokine signalling 3, which have anti-inflammatory effects by curtailing JAK and IL-6 activity (33,35). Thus, IL-6 exhibits pro-inflammatory and anti-inflammatory properties. Although the exact role of IL-6 in MAS is unknown, extended exposure to IL-6 may amplify the body's reaction to Toll-like receptor ligands, connecting high IL-6 in HLH to a worsened inflammatory response (12). Additionally, IL-6 may impair NK cell cytotoxicity by decreasing perforin and granzyme B expression, as observed in IL-6 transgenic mice (35).

Interleukin-18

A member of the IL-1 family, IL-18 is mainly produced by activated macrophages and stimulates NK cells and T cells to produce IFN-γ. Clinically, IL-18 serves as a marker for various HLH types and may indicate MAS risk in hyperferritinemia or autoinflammatory disorders (36). IL-18, which is somehow similar to IL-1β, remains inactive within cells until activated by caspase-1 (36). While IL-18 uses a different receptor than IL-1β, its signalling parallels IL-1β by activating the MyD88-IRAK1/4-NF-κB (IRAK-IL-1 receptor-associated kinase, nuclear factor-kappa B) pathway and mitogen-activated protein (p38-MAP) kinase upon binding to the receptors IL-18Rα and recruiting IL-18Rβ (20,36). However, distinct requirements exist; IL-18 needs additional stimulants (e.g., IL-12) to induce IFN-γ production, while IL-1β can activate diverse cells at much lower levels without added stimuli (37).

Tumor Necrosis Factor Alpha

Mostly produced by monocytes and macrophages, TNF-α is a polymorphic pro-inflammatory cytokine that is important in causing macrophages to polarize toward the M1 pro-inflammatory phenotype (15). According to a study examining the effect of recombinant TNF on NK cell activity in peripheral blood, specific lysis rates of NK cells decreased following treatment (38). While TNF-α is generally considered to promote the progression of HLH, there are instances where TNF-α inhibitors have been reported to indirectly induce HLH, thereby presenting a contradiction to its characterization as a positive regulator of the syndrome.

A study conducted by Baker et al documented 10 cases of MAS associated with the use of TNF-α inhibitors, such as etanercept, infliximab, and adalimumab (39). They found that the onset of MAS was temporally linked to the administration of these inhibitors, with patients developing MAS related to adalimumab approximately 2.5 months after treatment initiation. TNF-α inhibitor-

related MAS may be caused by immune system dysfunction and infections. Four individuals in the documented cases experienced liver abscesses, disseminated histoplasmosis, visceral leishmaniasis, and primary EBV infections after receiving adalimumab treatment (39).

Moreover, TNF-α can occasionally produce a paradoxical immune response, where immune suppression is followed by compensatory activation of the immune system (40). This imbalance can contribute to the development of MAS. Although there may be a relationship between TNF-α inhibitors and HLH, the evidence does not definitively establish the negative regulatory role of TNF-α. Accordingly, the underlying mechanisms warrant further investigation.

Interleukin-10

IL-10 is synthesized by various immune cells and has several functions as an immune regulator. It is categorized as one of the three principal subgroups in the IL-10 cytokine family. Further, IL-10 primarily communicates through the JAK-STAT signalling pathway, affecting a wide range of immune cell types and exerting strong anti-inflammatory effects (41). It modulates hemoglobin via the CD163 receptor on cell surfaces, leading to the production of IL-10 and heme oxygenase (HO-1) (42).

Additionally, IL-10 enhances the expression of CD163 on macrophages. In addition, HO-1 plays a vital role in breaking down heme, producing carbon monoxide and ferrous ions (Fe^{2+}), which contribute to anti-inflammatory responses (15). By suppressing the overall immune activity, IL-10 significantly influences HLH in a negative regulatory capacity.

Moreover, IL-10 impairs effective antigen presentation by reducing the expression of MHC-II and affecting the function of antigen-presenting cells. It inhibits the production of crucial cytokines (e.g., IL-12 and IL-23) for $CD4^+$ T cell differentiation and directly suppresses T cell proliferation and cytokine secretion, potentially leading to T cell anergy (43). Similarly, IL-10 can diminish the secondary immune responses of CD8 + ve T-cells (44). It is also known to inhibit the production of inflammatory mediators by neutrophils (45).

Considering that HLH is fundamentally characterized by an overwhelming inflammatory response, IL-10 may play a role in slowing its onset to some extent. Research has shown that mice with MAS induced by sustained CpG-oligodeoxynucleotide injection demonstrate a blockade of IL-10, which can worsen MAS (46).

Transforming Growth Factor Beta

The TGF-β ligand superfamily has 32 members. It is divided into TGF-β and bone morphogenetic proteins (47). The TGF-β subgroup is significant for immune system regulation. It acts via the TGF-β receptor II , which then recruits the TGF-β receptor I with the help of TGF-β receptor III, triggering the phosphorylation of the suppressors of mothers against decapentaplegic (Smad) protein family (48). The phosphorylated Smad2, Smad3, and Smad4 proteins form complexes that influence interactions within the nucleus and regulate transcription factors, leading to various cellular outcomes (49).

TGF-β also plays a vital role in maintaining immune system balance, particularly in regulating T-cell responses. It reduces autocrine IL-2 production, thereby inhibiting CD4 + T-cell proliferation (50). TGF-β activation of the Smad protein family restricts CTL cells from producing IFN-γ, perforin, granzyme, and Fas ligand (51). Furthermore, the Smad2 protein collaborates with other signalling pathways (e.g., STAT5 and nuclear factor of activated T-cells) to induce forkhead box protein P3 expression, promoting the differentiation of T-regulatory cells (Tregs) (52). Additionally, TGF-β downregulates the T-bet transcription factor and suppresses the differentiation of T-helper 1 cells (18, 53). It also inhibits NK-cell function through several mechanisms (54).

In general, TGF-β negatively regulates various immune cells while promoting the growth and differentiation of Tregs. By controlling the activities of T-cells and NK cells, TGF-β may help slow the progression of HLH.

Interleukin-2

T cells are the main source of IL-2, which is essential for activating Tregs and CTLs. In certain conditions (e.g., perforin deficiency), IL-2 levels can fluctuate, either increasing or decreasing. Hyperactivated CTLs often express elevated levels of the IL-2 receptor (also known as CD25), leading to greater IL-2 consumption. This increased usage by CTLs can deprive Tregs of IL-2, impacting their function and potentially disrupting immune balance (26). Similar to NK cells, the Treg population (CD4 + CD25 + T cells) plays an important role in the suppression of excessively activated immune cells. Impaired Treg function may promote the process of HLH.

Interleukin-33

In mice models of perforin-deficient HLH, IL-33 significantly amplifies immunological dysregulation (55). Notably, signalling through the IL-33/suppression of tumorigenicity 2 pathway has been shown to facilitate the activation of CTLs and the production of IFN-γ (55).

Clinical Implications of Cytokine Pathways in Hemophagocytic Lymphohistiocytosis

Diagnosis of Hemophagocytic Lymphohistiocytosis

Identifying and standardizing biochemical abnormalities in HLH offer exciting diagnostic and therapeutic opportunities. Well-known biochemical abnormalities (e.g., hyperferritinemia, hypertriglyceridemia, and hypofibrinogenemia) are not sensitive or specific to HLH. NK cell cytotoxicity and sCD25 levels, which are included in the HLH-2004 criteria, are unavailable in most centres, thereby reducing their practical application. The diagnosis of HLH still heavily relies on the clinician's judgement. It

is often delayed, and confusion arises between infection and HLH.

In a single-centre retrospective study from Canada, C-reactive protein (CRP) and ferritin levels were measured before commencing treatment for HLH, Adult-onset Still's disease (AOSD), or coronavirus disease-2019 cytokine storm (56). Ferritin levels did not vary significantly. A significantly lower level of CRP was noted in HLH patients compared to AOSD and coronavirus disease-2019 cytokine storm. A CRP below 94.5 mg/dL distinguished HLH with a sensitivity rate of 66.1% and specificity rate of 87.5% (56). It is noteworthy that even though median CRP values were lower, the range of CRP varied widely in this study.

A study conducted across multiple centres in Belgium from July 2014 to February 2016 measured the serum samples for ferritin, glycosylated ferritin, sCD25, sCD163 and sCD14, IL-6, IFN-γ, IL-18, IL-10, IL-1ß, IL-12p70, IL-17α, IFN-γ-induced protein 10, and chemokine-C-X-C motif ligand 9 in adult patients suspected to have HLH within the first 24 hours of admission (57). Out of 120 patients, 14 fulfilled the HLH-2004 criteria for HLH. Ferritin, IL-18, and glycosylated ferritin had the highest discrimination ability. The researchers combined IL-18 with the previously validated HScore, yielding a new IL-18Hscore. The new score performed better, with a higher specificity (86%) than HScore alone (70%) (10, 57).

Nonetheless, further biomedical research is warranted to identify a marker that can diagnose HLH at the bedside while being feasible to be performed at most centres.

Treatment of Hemophagocytic Lymphohistiocytosis

The survival time in genetic HLH without treatment is only around 1-2 months (58). Most adult patients with HLH are treated using pediatric protocols, such as the HLH-94 and HLH-2004. The HLH-94 protocol used dexamethasone, etoposide, and cyclosporine-A from week 9 with or without intrathecal methotrexate. Survival with the HLH-94 protocol improved to 55% at the 3.1-year follow-up (58). The HLH-2004 protocol utilized cyclosporine-A upfront, along with dexamethasone and etoposide (3). Hematopoietic stem cell transplantation (HSCT) is indicated in familial, severe, or refractory cases. The treatment of the underlying disorder is required in infection and malignancy-associated HLH and in MAS. The 5-year probability of survival after a median 5 years of follow-up was 61% (56–67%) (59). Overall, the 5-year probability of survival post-HSCT was 66% (59). Despite the less-than-desirable survival, conventional chemotherapeutics have significant toxicities. The discovery of key inflammatory cytokines has led to the investigation of targeted therapeutics for HLH. Possible therapeutic cytokine targets in HLH treatment are illustrated in Figure 2.

Targeting Interferon-Gamma

Emapalumab is a human immunoglobulin G1 monoclonal antibody against anti-IFN-γ. The Food and Drug Administration approved emapalumab in 2018 for pediatric and adult patients with primary HLH. It is the first targeted treatment approved for HLH. Studies evaluating the efficacy of emapalumab are listed in Table 1.

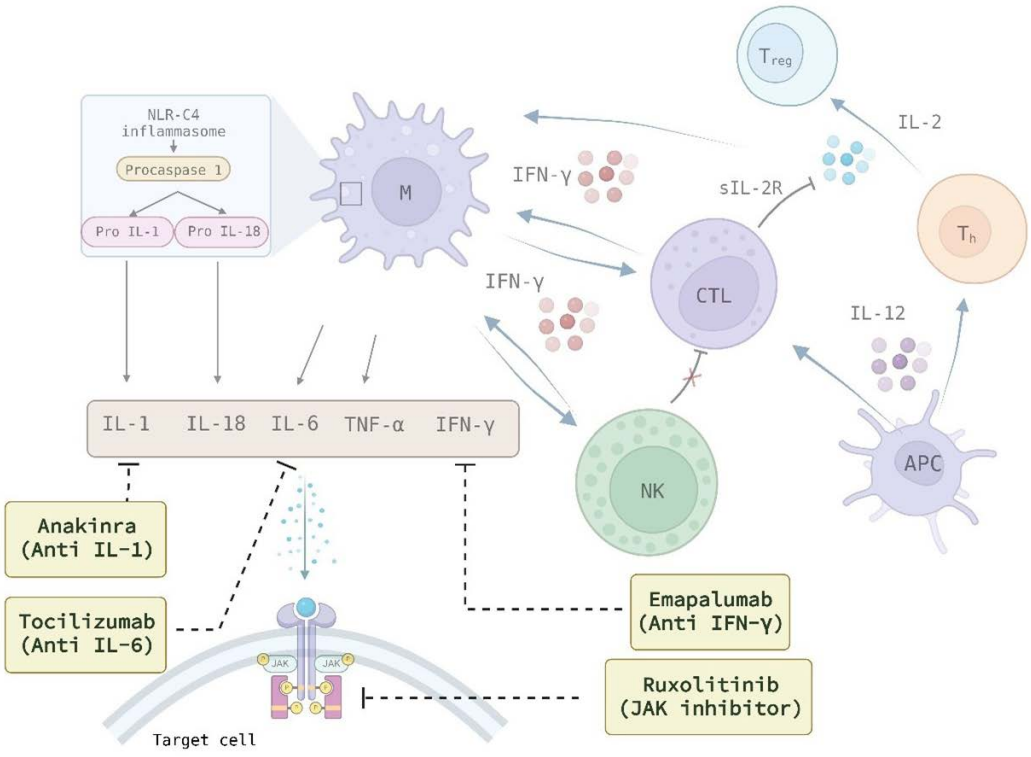

Figure 2. Therapeutic Targets in Hemophagocytic lymphohistiocytosis. Source. Created in BioRender. Punjadath, Sryla (2024). https://BioRender.com/p67r829

The safety and efficacy of emapalumab were published in a phase 2/3 trial (60). Thirty-four pediatric patients with presumed primary HLH were given emapalumab, along with dexamethasone, in an open-label single-group study. The study sample included 27 previously treated and 7 previously untreated patients. They were followed up until one year after the HSCT, or one year after the last dose of emapalumab, if HSCT was not performed. Nearly 65% of emapalumab-treated patients could proceed to transplantation. At the end of the study, 74% of previously treated patients and 71% of patients treated with emapalumab were alive, and there were no increased toxicities with emapalumab (60).

Emapalumab was also assessed in MAS secondary to AOSD/soJIA in a phase-2, open-label, single-group study, and the results revealed that this medication was effective in achieving remission by 8 weeks (61).

A recent retrospective study has focused on patients undergoing reduced-intensity conditioning before HSCT for primary HLH given emapalumab pre-HSCT (62). Out of 55 patients, 22 received emapalumab within 21 days of the conditioning regimen. Intervention-free survival was significantly higher in patients receiving emapalumab (73% vs. 43%, $P=0.03$). Overall survival did not differ significantly (62).

Ongoing trials (NCT03312751, NCT03985423) of emapalumab in primary and secondary HLH are yet to be reported (63, 64).

Targeting Janus Kinases

Downstream of the IFN-γ receptor activation, the JAK play an important role in signal transduction. Blocking the JAK pathway is an alternative to blocking the IFN-γ. It has the additional advantage of oral administration.

Ruxolitinib is a selective JAK1 and JAK2 inhibitor. It blocks the downstream signalling of IFN-γ in addition to several cytokines, such as IL-2, IL-6, IL-10, IL-12, and granulocyte monocyte-colony-stimulating factor. Studies evaluating the efficacy of ruxolitinib are provided in Table 2. Despite these studies, Severeal case studies have reported a favourable reponse to ruxolitinb when used as a salvage therapy, as described in this recent review article (65).

Two studies from the same centre reported a small case series of patients with secondary HLH treated with ruxolitinib, showing good responses to treatment (66,67).

In a study from China, 34 adult and pediatric patients with relapsed/refractory secondary HLH received ruxolitinib salvage therapy (69). Complete response and partial response were achieved by 5 patients and 20 patients, respectively. The rate of mortality was 44.4% (n = 15) after a median follow-up of 26.5 (15–52) weeks (69). The same group of investigators performed a trial of combined conventional doxorubicin-etoposide-methylprednisolone treatment with ruxolitinib as salvage therapy for relapsed/refractory HLH during a similar period (70). Of 54 patients, 8 achieved complete remission, while 31 achieved partial remission. Notably, patients with EBV-HLH had lower efficacy with combined therapy (70).

Researchers in Beijing, China, developed a novel treatment approach based on ruxolitinib (68). Ruxolitinib was used as a frontline therapy in pediatric patients with HLH. Monotherapy was continued for patients having a favorable response, while treatment was intensified in

Table 1. Clinical Trials of Emapalumab in HLH

Title and Reference Number	Year	Study Design	Population	Outcome
Emapalumab in children with primary hemophagocytic lymphohistiocytosis (60)	2020	Open-label; single arm	Children (<18 years) with primary HLH N = 34	Overall, 71% of patients treated with emapalumab stayed alive at one year; the results demonstrated no excess toxicity.
Efficacy and safety of emapalumab in macrophage activation syndrome (61)	2023	Open label; single arm	Patients with MAS secondary to soJIA or AOSD; median age = 11 years (range 2-25 years) N = 14	The efficacy outcome of remission, assessed at week 8, was achieved by 13 out of 14 patients.

Note. N denotes the sample size in the study. HLH: Hemophagocytic lymphohistiocytosis; AOSD: Adult-onset Still's disease; soJIA: Systemic onset juvenile idiopathic arthritis; MAS: Macrophage activation syndrome.

Table 2. Studies Evaluating the Efficacy of Ruxolitinib

Title and Reference Number	Year	Study Design	Population	Outcome
Ruxolitinib in adult patients with secondary haemophagocytic lymphohistiocytosis: an open-label, single-centre, pilot trial (66)	2019	Open-label, single centre, pilot study	Adults (age ≥ 18 years) secondary HLH N = 5 (still enrolling)	No deaths at the median follow-up of 490 days; one serious adverse event of grade-4 febrile neutropenia
Ruxolitinib in adult patients with secondary hemophagocytic lymphohistiocytosis (67)	2021	Open-label, single-centre	Adult (≥ 18 years) patients with secondary HLH N = 13	Three patients died, and five each achieved complete and partial remission.
A study of ruxolitinib response–based stratified treatment for pediatric hemophagocytic lymphohistiocytosis (68)	2022	Single-arm, open-label, single-centre	Paediatric patients (age ≤ 18 years) with newly diagnosed HLH N = 52	Response to ruxolitinib monotherapy on day 28 was 69.2%. Overall survival at 12 months for a ruxolitinib-based stratified approach was 86.4%.

Note. N represents the sample size in the study. HLH: Hemophagocytic lymphohistiocytosis.

others. Patients with EBV-HLH were found to be more sensitive to ruxolitinib. Out of 52 patients, 69.2% (n = 36) achieved complete remission on ruxolitinib monotherapy on day 28. The 12-month overall survival for this approach was 86.4% (95% confidence interval: 77.1–95.7%).

Other researchers tried a combination of targeted therapies. A retrospective analysis from a single centre reported 13 patients who received emapalumab and ruxolitinib for HLH treatment (71). All patients were adults (age > 18 years) with HLH of varied etiology. Eight patients had refractory/relapsed disease and had received previous treatment. At a median follow-up of 5.8 months, 5, 4, and 4 patients proceeded to allogeneic HSCT, died, and survived, respectively. Two patients who proceeded to HSCT died due to HSCT-related complications. The overall estimated survival at 5 months was 44.4% (71).

Targeting Cluster of Differentiation 52 (Alemtuzumab)

Alemtuzumab is a humanized anti-CD52 monoclonal antibody that depletes B cells and T cells from the peripheral blood circulation without depleting the hematopoietic progenitor cells. It is used in the management of chronic lymphocytic leukemia, T-cell large granular leukemia, multiple sclerosis, refractory aplastic anemia, conditioning regimen in HSCT, and graft treatment against host disease.

A single-centre retrospective study of patients who received alemtuzumab for refractory HLH was performed in 2013 (72). Twenty-two adult and pediatric patients who had previously received conventional HLH therapies were given alemtuzumab 1 mg/kg divided over 4 days. In addition, 11 patients required additional doses of alemtuzumab following the initial dose, of whom 3 died, 2 required additional salvage therapy, and 7 proceeded to HSCT. Overall, 14 patients had an overall partial response, and 17 patients proceeded to HSCT. The probability of survival following alemtuzumab salvage therapy at a median of 870 days was 64% (+ /- 21%) (72).

A multicentre, open-label, Phase I/II non-randomised trial of alemtuzumab in primary HLH was conducted in Paris. The researchers reported that 26 patients received alemtuzumab retrospectively. In the retrospective study, 24 out of 26 patients proceeded to HSCT. In the prospective study, twenty-nine treatment naïve patients with genetically confirmed primary HLH were given first-line alemtuzumab alongside steroids and cyclosporin A. Twenty-two patients survived until HSCT (73).

Alemtuzumab has demonstrated variable responses in patients with HLH as both primary and salvage therapies. It may be used off-label in HLH. More evidence is required regarding its safety. It is noteworthy that this antibody medication can notoriously induce several autoimmune diseases, including HLH (74, 75).

Targeting Interleukin-6

IL-6 is a cytokine elevated in patients with HLH. As discussed earlier, the role of IL-6 in HLH is unclear. This cytokine has positive and negative regulatory roles in HLH.

Tocilizumab is an IL-6 receptor inhibitor. It may be effective as a treatment for cytokine release syndrome (76). It is the cornerstone in the management of chimeric antigen receptor-T-cell-induced CRS (77). Moreover, it dampens the action of effector cytokines without compromising the function of chimeric antigen receptor-T cells.

For this reason, or due to as yet unclear mechanisms, tocilizumab has not been an effective therapy in HLH. Treatment with this medication in patients with soJIA did not reduce the occurrence of MAS (78). The results of a retrospective study of secondary HLH patients receiving tocilizumab in Korea revealed a trend toward higher mortality as compared to patients receiving standard care (79). It is noteworthy that IL-6 has an as yet ambiguous role in HLH and has several pro-inflammatory and anti-inflammatory properties.

Targeting Interleukin-1

Anakinra is a recombinant human IL-1 receptor antagonist. Nine of the 13 individuals with HLH attributable to acute leukemia in a retrospective assessment did not experience the recurrence of HLH after receiving anakinra initially (80). The use of anakinra in six children with secondary HLH also showed promising results (81). A retrospective analysis of 44 children with secondary HLH or MAS treated in a single centre in Alabama demonstrated that the earlier initiation of anakinra (within 5 days) was associated with reduced mortality (82). Another retrospective analysis of adult patients with secondary HLH reported 30 patients who received the HLH-94 protocol, anakinra and high-dose steroids, high-dose steroids alone, and supportive care only (83). Compared to other groups, those receiving anakinra with high-dose steroids had numerically higher survival at 1 year (83).

Targeting Interleukin-18

Tadekinig-α is a recombinant IL-18 binding and neutralizing protein. It has shown promising results in the treatment of AOSD (84, 85). A phase-3 clinical trial (NCT03113760), assessing the efficacy of tadikinig-α in primary HLH with nucleotide-binding oligomerization domain, leucine-rich repeat and caspase-recruiting domain containing-4 mutations, and X-linked inhibitor of apoptosis deficiency, completed recruitment, and the results are awaited (86).

Conclusion

In general, HLH remains a highly fatal immune disorder characterized by aggressive immune activation and cytokine storm. Despite advancements in understanding the pathophysiology of HLH, including the involvement of key cytokines (e.g., IFN-γ, TNF-α, and IL-18), challenges in diagnosis and treatment persist. Current diagnostic criteria (e.g., the HLH-2004 protocol) are insufficiently specific and often delay diagnosis, especially in adult

populations where HLH may be under-recognized.

Biochemical mediators have opened new avenues for targeted therapies, with emapalumab representing a breakthrough as an IFN-γ inhibitor approved for the refractory cases of HLH. Nevertheless, survival rates, particularly in severe and genetic HLH cases, highlight the urgent need for better therapeutic strategies and early diagnostic markers. Ongoing research into cytokine profiles (e.g., the IL-18 HScore) and the use of newer treatments (e.g., monoclonal antibodies) offer hope for improving outcomes. Nonetheless, more extensive studies are required to validate these tools in diverse clinical settings and broaden their accessibility, especially in resource-limited environments. Understanding the full biochemical basis and integrating precision medicine in HLH management can also revolutionize patient care and long-term survival outcomes.

Authors' Contribution

Conceptualisation: Ravi Kant.
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Writing-review & editing: Sryla Punjadath, Ravi Kant.

Competing Interests

The authors declare no competing interests.

Ethical Approval

Considering that this was a narrative review, no ethics committee clearance was required to write this article.

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