Received: 31 August 2016 | Revised: 19 September 2016 | Accepted: 20 September 2016

DOI: 10.1002/pbc.26308

REVIEW

WILEY Pediatric Blood & Cancer

SIOP INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY

aspho The American Society of Pediatric Hematology/Oncology

Salvage therapy for refractory hemophagocytic lymphohistiocytosis: A review of the published experience

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Abstract

Hemophagocytic lymphohistioytosis (HLH) is a severe, life-threatening hyperinflammatory disorder that requires prompt diagnosis and treatment. Approximately, 25–50% of patients with HLH fail to achieve remission with established regimens that include dexamethasone and etoposide, or methylprednisolone and antithymocyte globulin (ATG). Some of these patients may require salvage or alternative therapeutic approaches. There is a paucity of literature regarding effective salvage therapies for patients with refractory HLH. In this review, we summarize the published experience of four therapeutics reported for using at least two patients with HLH refractory to dexamethasone and etoposide or methylprednisolone and ATG.

KEYWORDS

hemophagocytic lymphohistiocytosis, HLH, refractory HLH, salvage therapy

1 | INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a severe, life-threatening hyperinflammatory clinical syndrome classically characterized by fevers, cytopenias, and hepatosplenomegaly. Additionally, some patients may develop other clinical manifestations such as hepatitis, liver dysfunction, and central nervous system involvement.[1] Several typical laboratory manifestations are often observed including elevated ferritin, soluble IL2R, and triglyceride levels, and low levels of fibrinogen.

Genetic diseases that primarily manifest with the development of HLH are often grouped together as "primary HLH" (Table 1). Most of these diseases are caused by mutations in genes that cripple cytotoxic lymphocyte granule-mediated cytotoxicity,[2–7] although X-linked lymphoproliferative disease type 1 (XLP1 because of mutations in *SH2D1A*) and XLP type 2 (XLP2 because of mutations in *BIRC4*) are associated with alternative mechanisms of disease.[8–11] Other primary immune deficiencies can also be associated with the development of HLH.[12] Outside these known genetic disorders, patients may develop HLH that is due to an as-of-yet undiscovered genetic defect, and be presumed to have primary HLH due to family history or the recurrence of disease over time. Many patients lack an obvious genetic etiology for HLH predisposition, and develop what is referred to as "secondary HLH." Secondary HLH is thought to be triggered in normal individuals by severe infections or malignancies, or to occur in patients with immune compromise due to immunosuppressive treatment or underlying autoimmune diseases such as systemic onset juvenile idiopathic arthritis (where HLH is commonly referred to as macrophage activation syndrome [MAS]). Regardless of HLH etiology,

Abbreviations: ATG, antithymocyte globulin; DEP, doxorubicin, etoposide, and methylprednisolone; HCT, hematopoietic cell transplantation; HLH, hemophagocytic lymphohistiocytosis; MAS, macrophage activation syndrome

TABLE 1 Genetic causes of primary HLH

Gene	Protein	Disease
PRF1	Perforin	Familial lymphohistiocytosis type 2
UNC13D	Munc13-4	Familial lymphohistiocytosis type 3
STX11	Syntaxin-11	Familial lymphohistiocytosis type 4
STXBP2	Syntaxin-binding protein 2	Familial lymphohistiocytosis type 5
RAB27A	Ras-related protein Rab-27A	Griscelli syndrome type 2
LYST	Lysosomal trafficking regulator	Chediak-Higashi syndrome
SH2D1A	Signaling lymphocytic activation molecule (SLAM) associated protein (SAP)	X-linked lymphoproliferative syndrome type 1
BIRC4	X-linked inhibitor of apoptosis (XIAP)	X-linked lymphoproliferative syndrome type 2

TABLE 2 Established treatment strategies for HLH and success

Primary treatment regimen	Reference	N	CR	PR	NR	Died and not included in response assessment	Relapses following CR
HLH-1994	Henter et al.	113	56 (53%)	34 (32%)	4 (4%)	12 (11%)	7
ATG (rabbit), MP	Mahlaoui et al.	38 (45 courses)	33 (73%)	11 (24%)	1 (2%)		8

CR, complete response; PR, partial response; NR, no response; ATG, antithymocyte globulin; MP, methylprednisolone.

HLH is life-threatening and patients require prompt diagnosis and treatment to prevent death.

HLH is traditionally managed by one of two established immunosuppressive therapeutic regimens that contain corticosteroids with either etoposide or antithymocyte globulin (ATG) (Table 2).[13,14] Dexamethasone and etoposide were combined in a prospective trial initiated by the Histiocyte Society in 1994 (HLH-1994).[13] Cyclosporine was added during the continuation phase of treatment. In an interim report including 113 patients, after 2 months of therapy resolution of HLH was observed in 53% of patients (some of whom had had a reactivation), improvement was observed in an additional 32%, while no improvement was observed in 4% of the patients. Of the patients who died during the entire initial and continuation therapy (n = 25), 20 were related to disease and 4 to toxicity.

An immunotherapeutic approach for HLH that lacked chemotherapy was pioneered in France, which combined ATG (rabbit) and methylprednisolone.[14] Cyclosporine was also added in the maintenance phase. With this approach, 73% of patients achieved a complete response, but 24% of patients achieved only a partial response and 2% failed to respond. Notably, of the eight patients, who showed clinical remission following the first course of ATG but did not proceed to allogeneic hematopoietic cell transplantation (HCT), all experienced a relapse of HLH.

Based on the above results, it is clear that approximately 25–50% of patients will fail to achieve a complete response to standard-of-care therapy and may require additional treatment with the same drugs or alternative "salvage" agents. Additionally, patients who respond to therapy initially may experience a relapse of HLH. Relapses may respond to intensification of standard-of-care therapy,[13,14] or may require additional or alternative therapies.

Currently, there is limited literature concerning the salvage therapy of patients with resistant or recalcitrant disease, and there are no consensus guidelines regarding treatment options. Additionally, the very definition of refractory disease is itself challenging, given that patients with familial HLH can be expected to experience frequent reactivations, as therapies are weaned. In order to address these challenges, a Salvage Therapy Working Group was formed within the Histiocyte Society to review the published experience with salvage therapies for patients with relapsed or refractory HLH. A summary of the data is presented in this paper.

2 | METHODS

2.1 | Literature review

Members of the working group reviewed the literature via PubMed search strategies. Search terms included HLH or MAS and therapy, treatment, salvage, or specific treatment agent names including alemtuzumab, tocilizumab, etanercept, infliximab, adalimumab, rituximab, anakinra, canakinumab, daclizumab, basiliximab, ATG, tacrolimus, sirolimus, cyclosporine, and doxorubicin. Articles were reviewed if written in English and if published in the year 2000 or later. Articles referenced in the reviewed articles were also examined. We included articles in this review, if the agent(s) used was(were) given to at least two patients who were previously treated with the established therapies of either steroids and etoposide, or steroids and ATG. Patients may have continued on previous therapeutic agents while receiving salvage therapy. Patients with primary and secondary forms of HLH were included except for patients with malignancy-associated HLH, who were excluded.

2.2 | Assessment of refractory disease

The definition of refractory HLH is difficult, and no standard definition has been widely accepted. Refractory HLH can be considered as failing to experience an adequate response to conventional therapy,[15] though

this can be widely interpreted. Some authors have defined refractory HLH to be the failure to achieve at least a partial response 2 weeks following standard HLH therapy.[16] For the purpose of this review, we accepted that patients were considered to have refractory disease as reported by the authors.

2.3 | Assessment of response

For case reports, we accepted that patients experienced complete response or partial response as reported by the authors. For larger case series, complete and partial response definitions were reported by clinical criteria as described by the authors and are summarized in Table 3.

3 | RESULTS

3.1 | Literature review

Many agents have been reported to have been used for patients with refractory HLH. We limited our review to salvage agents given to at least two patients previously treated with the established therapies of steroids and etoposide or steroids and ATG, as described in Section 2. Agents that met our criteria for inclusion in this review included anakinra, ATG, alemtuzumab, and a regimen consisting of liposomal doxorubicin, etoposide, and methylprednisolone (DEP).

3.2 | Efficacy of salvage therapeutics

3.2.1 | Anakinra

Three patients with rheumatologic/autoimmune disorders and "secondary HLH or MAS" received anakinra for salvage therapy of HLH following treatment with steroids and etoposide (Table 4).[17,18] The first was a 14-year-old patient with cytophagic histiocytic panniculitis and secondary HLH initially treated with methylprednisolone (1 g daily), a single dose of etoposide, and cyclosporine.[17] Three days following etoposide, the patient remained unchanged, and anakinra (2 mg/kg/day) was started. Her laboratory data and mental status improved within 2 days; she could be extubated and required no further blood transfusions. Organomegaly was resolved within 1 week following anakinra. The patient was reported to remain in remission for 6 months at the end of the reported follow-up.

In the second report on the use of anakinra in patients with rheumatologic-associated HLH/MAS, two patients were treated with anakinra following methylprednisolone, cyclosporine, and etoposide.[15] No information regarding the diagnosis of HLH/MAS was given specifically for these two patients, or the details regarding length of the treatment prior to anakinra were also not provided. One of the patients was diagnosed with Kawasaki disease and the other patient was diagnosed with systemic juvenile idiopathic arthritis (sJIA). Both patients were reported to experience a complete resolution of HLH by 10 days following the initiation of anakinra, and maintained their responses to last follow-up of 5 or 24 months (Table 4).

3.2.2 | ATG (rabbit)

Within the original French report of rabbit ATG (Genzyme) as treatment for familial HLH (Mahlaoui et al.[14]), two patients received ATG as second-line therapy following steroids and etoposide (Table 4). Their results were reported together with eight additional patients who received ATG as the second-line therapy following other treatment regimens.[14] The dose of rabbit ATG was reported for all patients as 25 or 50 mg/kg according to the severity of disease, divided over five consecutive days. Methylprednisolone at a dose of 4 mg/kg per day was given with the ATG and then tapered. Within the group of 10 patients, 5 of 10 achieved a complete response and 4 of 10 achieved a partial response. When specifically queried, the authors report that the two patients, who were treated with ATG following steroids and etoposide, achieved a complete response (Alain Fischer, personal communication).

Mahlaoui et al. also reported the outcomes of a second round of rabbit ATG that was administered to seven patients following a previous course of ATG (in six patients following a complete response and relapse, and in one patient following a partial response and relapse).[14] Of those seven patients, six patients achieved a complete response and one patient achieved a partial response (Table 4).

3.2.3 | Alemtuzumab

Two case reports and one retrospective case series described the use of alemtuzumab for patients with refractory HLH. The first case report by Strout et al. described an adult with HLH, who was initially treated with intravenous immunoglobulin, cyclosporin, dexamethasone, infliximab, dexamethasone, and etoposide.[19] One week following alemtuzumab, the patient's fever resolved, blood counts were reported to improve but not normalize, and the lymphohistiocytic infiltrate on bone marrow biopsy resolved (partial response) (Table 4). A second case report (Gerard et al.) described an adult with HLH previously treated with dexamethasone, cyclosporine, etoposide, intravenous immune globulin, methylprednisolone, and plasmapheresis.[20] Cyclosporine was held due to nephrotoxicity, and etoposide dosing was reduced due to biopsy-proven hepatic sinusoidal necrosis toxicity. This patient received 30 mg alemtuzumab subcutaneously thrice a week and was reported to experience a normalization of the absolute neutrophil count within 1 week, and also experienced a rise in the platelet count to 50×10^9/l and a fall of ferritin from 4,756 to 1,500 μg/l by 2 weeks (partial response) (Table 4).

A larger case series (n = 22) of pediatric and young adult patients, who received alemtuzumab for salvage therapy of primary HLH, was also reported.[15] All patients in this series had previously received dexamethasone and etoposide. Twenty-three percent of patients did not receive etoposide in the 2 weeks prior to alemtuzumab due to intolerance (marrow suppression/neutropenia). Additional therapies received during the 2 weeks just prior to alemtuzumab included cyclosporine, intrathecal hydrocortisone ± methotrexate, methylprednisolone, and rituximab in 36%, 23%, 9%, and 14% of patients, respectively. A wide range of alemtuzumab dosing was administered with a median dose of 1 mg/kg, typically administered subcutaneously and divided over a median of 4 days as the first or only course. No patients

TABLE 3 Definitions or descriptions of complete and partial responses in reviewed literature

Salvage agent and reference	N	Partial response description or definition	Complete response description or definition
Anakinra			
Behrens et al.	1		Improvement in laboratory studies, no need for further blood transfusions, improvement in mental status, resolution of organomegaly.
Miettunen et al.	2 (following steroids and etoposide)		Resolution of MAS
ATG (rabbit)			
Mahlaoui et al.	2 (following steroids and etoposide) 7 (following previous steroids and ATG)	A significant but incomplete improvement of clinical and/or biological manifestations of HLH. Clinical manifestations included mainly fever, hepatosplenomegaly, neurologic symptoms, and bleeding. Biological manifestations included cytopenia, hypertriglyceridemia, hypofibrinemia, hyperferritinemia; high blood levels of liver enzymes, cerebrospinal pleocytosis, or high levels of protein, and excess HLA DR + CD8+ T cells in the blood and/or cerebrospinal fluid.	Complete disappearance of clinical and biological signs of HLH. Clinical manifestations included mainly fever, hepatosplenomegaly, neurologic symptoms, and bleeding. Biological manifestations included cytopenia, hypertriglyceridemia, hypofibrinemia, hyperferritinemia; high blood levels of liver enzymes, cerebrospinal pleocytosis or high levels of protein, and excess HLA DR + CD8+ T cells in the blood and/or cerebrospinal fluid.
Alemtuzumab			
Strout et al.	1	Fever resolved, blood counts improved but platelets did not normalize, lymphohistiocytic infiltrate on bone marrow biopsy resolved.	
Gerard et al.	1	Normalization of the absolute neutrophil count, a rise in the platelet count to 50×10^9/l, a fall of ferritin from 4,756 to 1,500 μg/l, and regression of hemophagocytosis in marrow samples.	
Marsh et al.	22	At least 25% improvement in two or more quantifiable symptoms and laboratory markers by 2 weeks following alemtuzumab as follows: Soluble IL-2 receptor response was defined as a greater than a 1.5-fold decrease. Ferritin and triglyceride responses were defined as decreases of at least 25%. For patients with an initial absolute neutrophil count (ANC) of less than 0.5×10^9/l, a response was defined as an increase in at least 100% to greater than 0.5×10^9/l. For patients with an ANC of $0.5–2.0 \times 10^9$/l, a response was defined as an increase in at least 100% to more than 5×10^9/l. For patients with transaminitis with an ALT greater than 400 U/l, an ALT response was defined as a decrease of ALT of at least 50%. For patients with hemophagocytosis noted on a biopsy specimen within 4 weeks of alemtuzumab, a response was defined as resolution of hemophagocytosis following alemtuzumab. For patients with refractory CNS HLH and altered level of consciousness, a response was defined as a normal level of consciousness following alemtuzumab.	Normalization of all listed at left.
DEP			
Wang et al.	34 (patients with lymphoma-associated HLH were excluded here)	At least a 25% improvement in two or more quantifiable symptoms and laboratory markers by 2 weeks following DEP regimen as follows: A sCD25 response was considered as a 1.5-fold or more decrease. Response of ferritin and triglyceride was considered as a decrease of at least 25%. For patients with an initial neutrophil count of $<0.5 \times 10^9$/l, a response was defined as an increase in at least 100% to $>0.5 \times 10^9$/l. For patients with a neutrophil count of $0.5–2.0 \times 10^9$/l, an increase in at least 100% to $>2.0 \times 10^9$ was considered a response. For patients with an ALT above 400 U/l, response was defined as an ALT decrease of at least 50%. Fever resolution.	Normalization of all of the quantifiable symptoms and laboratory markers of HLH, including levels of sCD25, ferritin, and triglyceride; hemoglobin; neutrophil counts; platelet counts; and alanine aminotransferase (ALT). Fever resolution.

TABLE 4 Salvage therapy regimens and responses

Salvage agent	N	Dosing regimen(s)[a]	Time of response assessment or description of response	CR	PR	NR
Anakinra						
Behrens et al.	1	2 mg/kg/day	1 week (less for some symptoms)	1		
Miettunen et al.	2 (12 patients reported in the series but only 2 received anakinra following steroids and etoposide)	2 mg/kg/day	10 days	2		
ATG (rabbit)						
Mahlaoui et al.	2 (2 received ATG following steroids and etoposide) 7 (following previous steroids and ATG)	ATG: 25 or 50 mg/kg divided over five consecutive days. Methylprednisolone: 4 mg/kg/day given with the ATG and then tapered.	For all patients included in the report (n = 38, 45 courses) CR was achieved in a median time of 8 days (range, 4–15 days)	2 6	 1	
Alemtuzumab						
Strout et al.	1	30 mg subcut thrice a week	1 week		1	
Gerard et al.	1	30 mg subcut thrice a week	1 and 2 weeks		1	
Marsh et al.	22	Median 1 mg/kg (range, 0.1–8.9 mg/kg) divided over a median of 4 days (range, 2–10 days) as a first or only course	2 weeks		14	8[b]
DEP						
Wang et al.	34 (patients with lymphoma-associated HLH were excluded here)	In the first month: Liposomal doxorubicin 25 mg/m^2 on day 1. Etoposide 100 mg/m^2 on the first day of every week. Methylprednisolone 15 mg/kg, days 1–3; 2 mg/kg, days 4–6; 1 mg/kg, days 7–10; 0.75 mg/kg, days 11–14; 0.5 mg/kg, days 15–21; and 0.4 mg/kg, days 22–28	2 and 4 weeks	12	14	8

CR, complete response; PR, partial response; NR, no response.
[a]Many patients were also continued on previous HLH-directed therapies.
[b]Some patients had improvement in one sign or symptom of HLH.

in this series experienced a complete response, though the follow-up time was limited due to allogeneic HCT and the assessment of response was performed at 2 weeks. A partial response was achieved in 14 of 22 patients (64%) (Table 4). The remaining patients failed to respond or had improvement in only one sign or symptom of HLH. Seventy-seven percent of patients survived to undergo allogeneic hematopoietic cell transplantation.

3.2.4 | Combination chemotherapy with DEP

Wang et al. reported a prospective study of liposomal DEP for patients 18 years and older with HLH, who failed to achieve at least a partial remission after 2 or more weeks of HLH-94 treatment with (in patients with EBV-HLH) or without rituximab.[16] The median time from initial therapy to receipt of DEP regimen was 3 weeks (range, 2–28 weeks). The authors enrolled 63 patients, and we reviewed their experience in 34 patients after we excluded patients with lymphoma-associated HLH (Table 4). Twelve of 34 patients achieved a complete response (35%), 14 patients achieved a partial response (41%), and 8 patients failed to respond (24%) (Table 4).

3.3 | Toxicities and complications

3.3.1 | Anakinra

No toxicities or complications were reported in the three patients who received anakinra, and the authors reported that no side effects following administration were observed.[17,18]

3.3.2 | ATG (rabbit)

Toxicities and complications were not reported individually for the patients who received ATG following either dexamethasone and etoposide or a previous course of steroids and ATG. However, for the 45 courses of ATG as a whole, 20 were complicated by immediate adverse effects including fever and chills (40%), neutropenia (16%), neurologic symptoms (4%, one patient with seizures and one patient with pyramidal irritation), or other (11%) complications.[14] No interruption of ATG was required, and all adverse effects were resolved. Infections following ATG occurred in 22% of the group as a whole, including bacterial, fungal, and viral infections. Epstein–Barr Virus (EBV) associated lymphoproliferative disorder was observed in three patients. Death was observed in four patients either due to

disseminated fungal infection or EBV-induced B lymphoproliferative disorder.

3.3.3 | Alemtuzumab

Adverse reactions to alemtuzumab were not mentioned in the two reviewed case reports with the exception of fulminant polymicrobial sepsis in one patient, as reported by Gerard et al., 3.5 months following alemtuzumab.[20] In the case series of 22 patients treated with alemtuzumab, 4 experienced fever, 1 experienced urticaria, 4 experienced transient worsening of neutropenia, and 2 experienced transient worsening of thrombocytopenia.[15] Nine patients experienced bacteremia or candidemia. Viral reactivations were common: CMV viremia was reported to occur in 14% of patients before alemtuzumab and 32% of patients following alemtuzumab. Adenovirus viremia was reported to occur in 0% of patients prior to alemtuzumab and 23% of patients following alemtuzumab. EBV viremia occurred in 36% of patients prior to alemtuzumab and 23% of patients following alemtuzumab. No patients displayed evidence of EBV-associated lymphoproliferative disease.

3.3.4 | DEP

In the study of DEP, the authors found it difficult to evaluate marrow toxicity because patients were cytopenic at the onset of therapy.[16] However, they noted transient worsening of cytopenias in a minority of patients at 2 weeks following DEP, which improved by 4 weeks, and all patients who had a repeat marrow following DEP displayed recovering bone marrow function with bone marrow hyperplasia. The authors concluded that they did not observe evidence of bone marrow toxicity directly associated with the regimen. The authors also report that they did not observe new infections directly induced by the DEP regimen or aggravation of preexisting infections.

4 | DISCUSSION

In this manuscript, we reviewed the literature regarding salvage therapeutic approaches for patients with refractory HLH and found only limited evidence for a few therapeutics. Although many reports exist, only four approaches were found in the literature that included a minimum of two patients with HLH refractory to the established therapies of steroids and etoposide or steroids and ATG.

Anakinra appears to be a promising choice for patients with refractory rheumatologic associated HLH given the good responses observed and the lack of significant side effects or toxicities observed in the three reported patients.[17,18] However, the published experience is limited to only three patients who were previously treated with established HLH therapies. Additionally, we did not find any reports of anakinra used as salvage therapy for patients with primary HLH. Thus, there is no published experience upon which to base consideration of anakinra in patients with refractory forms of primary or nonrheumatologic HLH.

ATG appears to have a good complete response rate in patients with refractory HLH, who were initially treated with a variety of agents, but only two patients have been treated following steroids and etoposide, which limits the conclusion.[14] The high rates of adverse effects, infections, and EBV-associated lymphoproliferative disease are a concern with its use given that these complications were sometimes fatal. However, these complications are likely less of a concern when ATG is used with the intention of bridging the patient to an upcoming allogeneic HCT.

Alemtuzumab was associated with partial responses in the majority of patients, but there were no complete responses reported.[15,19,20] However, the response observation time was limited to 2 weeks in the larger case series given that most patients moved quickly to allogeneic HCT.[15] There may have been a patient population bias in that series since all patients were treated at tertiary referral centers and therefore may have had a worse and late stage of disease, having exhausted primary resources before referral. Notably, adverse effects were sometimes noted (fever, urticaria, cytopenias) and infections were common following alemtuzumab, including a notable incidence of CMV and adenovirus viremias. EBV viremia was not increased in patients following alemtuzumab, and alemtuzumab may offer some protection against the development of EBV-associated lymphoproliferative disease compared to ATG since alemtuzumab depletes B cells as well.

The DEP regimen was associated with a complete or partial response in approximately 75% of patients, with very little toxicity or complicating infections reported.[16] However, the regimen was used exclusively in adult patients, most of whom did not have primary HLH, and so its usefulness in pediatric or young adult patients with refractory primary HLH setting remains uncertain. Additionally, the regimen is similar to standard-of-care dexamethasone and etoposide alone, and it is possible that with more time, some of the patients treated in the DEP study would have been observed to respond to dexamethasone and etoposide. A randomized clinical trial with the comparison of DEP to dexamethasone and etoposide would be required to determine if response rates at 4 weeks are better with the DEP regimen compared to continued therapy with dexamethasone and etoposide alone.

Overall, there is a lack of adequate literature upon which to confidently base decisions regarding salvage therapy of HLH or predict outcomes of patients with refractory HLH. Prospective clinical trials of salvage and/or alternative therapies are urgently needed. One such trial is ongoing in Europe and the United States, involving a targeted anti-interferon gamma monoclonal antibody (NI-0501, Novimmune). Preliminary results of this trial were recently reported in abstract form[21] and appear promising. Final results of this trial and whether this agent gains regulatory approval for the treatment of HLH will likely have a significant impact on future salvage strategies and trials. Alemtuzumab and tocilizumab are currently being prospectively studied in centers in France and the United States, respectively. Ruxolitinib may also hold promise as an alternative or salvage therapy for patients with HLH based on preclinical murine data,[22,23] and a pilot study for secondary HLH is open in the United States (ClinicalTrials.gov Identifier: NCT02400463). Future results regarding the use of these and other agents will hopefully lead to improved outcomes for patients with refractory HLH.

ACKNOWLEDGMENTS

The authors wish to thank the members of the Histiocyte Society Steering Committee for helpful discussions and guidance regarding the manuscript. All authors contributed to the design of the study, literature review, and writing and/or editing of the manuscript.

CONFLICT OF INTEREST

MBJ is associated with the consultancy, Novimmune. The remaining authors declare that there is no conflict of interest.

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