

ORIGINAL ARTICLE

Emapalumab in Children with Primary Hemophagocytic Lymphohistiocytosis

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ABSTRACT

BACKGROUND

Primary hemophagocytic lymphohistiocytosis is a rare syndrome characterized by immune dysregulation and hyperinflammation. It typically manifests in infancy and is associated with high mortality.

METHODS

We investigated the efficacy and safety of emapalumab (a human anti-interferon- γ antibody), administered with dexamethasone, in an open-label, single-group, phase 2–3 study involving patients who had received conventional therapy before enrollment (previously treated patients) and previously untreated patients who were 18 years of age or younger and had primary hemophagocytic lymphohistiocytosis. The patients could enter a long-term follow-up study until 1 year after allogeneic hematopoietic stem-cell transplantation or until 1 year after the last dose of emapalumab, if transplantation was not performed. The planned 8-week treatment period could be shortened or extended if needed according to the timing of transplantation. The primary efficacy end point was the overall response, which was assessed in the previously treated patients according to objective clinical and laboratory criteria.

RESULTS

At the cutoff date of July 20, 2017, a total of 34 patients (27 previously treated patients and 7 previously untreated patients) had received emapalumab; 26 patients completed the study. A total of 63% of the previously treated patients and 65% of the patients who received an emapalumab infusion had a response; these percentages were significantly higher than the prespecified null hypothesis of 40% ($P=0.02$ and $P=0.005$, respectively). In the previously treated group, 70% of the patients were able to proceed to transplantation, as were 65% of the patients who received emapalumab. At the last observation, 74% of the previously treated patients and 71% of the patients who received emapalumab were alive. Emapalumab was not associated with any organ toxicity. Severe infections developed in 10 patients during emapalumab treatment. Emapalumab was discontinued in 1 patient because of disseminated histoplasmosis.

CONCLUSIONS

Emapalumab was an efficacious targeted therapy for patients with primary hemophagocytic lymphohistiocytosis. (Funded by NovImmune and the European Commission; NI-0501-04 and NI-0501-05 ClinicalTrials.gov numbers, NCT01818492 and NCT02069899.)

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HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS is a rare disorder characterized by pathologic immune activation and hyperinflammation with deleterious effects on multiple organs.^{1,2} Primary hemophagocytic lymphohistiocytosis is a heterogeneous disorder that is associated with impaired cytotoxic function of natural killer and CD8+ T cells. It typically manifests during infancy and is invariably fatal if untreated.^{1,3,4}

The objective of treatment for primary hemophagocytic lymphohistiocytosis is to suppress inflammation in order to allow for allogeneic hematopoietic stem-cell transplantation, the only curative therapy for this disease. Various immunochemotherapeutic regimens have been tested.⁵⁻⁷ No drug has been approved for hemophagocytic lymphohistiocytosis, but glucocorticoids and etoposide, with or without cyclosporine, investigated by the Histiocyte Society,^{5,6} have become the conventional therapy. Despite the use of increasingly aggressive regimens, no significant decrease in mortality (it was approximately 40% as of this writing) has been noted over the past 20 years.⁵⁻⁷ Toxic effects of immunochemotherapy, particularly myelosuppression and generalized immunosuppression, contribute to high morbidity and mortality.^{5,6} Among patients with disease flares, proposed reintensification with etoposide⁸ increases the risk of toxic effects.

No standardized treatment exists for relapsed or refractory hemophagocytic lymphohistiocytosis; however, individual case reports involving patients who have received biologics and small case series involving patients who have received alemtuzumab (an anti-CD52 monoclonal antibody) and antithymocyte globulin have shown efficacy in some patients.⁹⁻¹² Mounting evidence provides support for the pivotal pathogenic role of interferon- γ in hemophagocytic lymphohistiocytosis. Elevated interferon- γ levels in patients with hemophagocytic lymphohistiocytosis correlate with active disease,^{4,13-16} and neutralization of interferon- γ in models of hemophagocytic lymphohistiocytosis in mice allowed most of the mice to survive, reduced signs and symptoms, or both.¹⁶⁻²⁰ Targeting other cytokines does not result in these outcomes.

Emapalumab is a fully human IgG1 anti-interferon- γ monoclonal antibody that binds free and receptor-bound interferon- γ (inhibiting recep-

tor dimerization and transduction of interferon- γ signaling) and neutralizes its biologic activity.²¹ We prospectively tested the safety and efficacy of multiple intravenous doses of emapalumab on a background of dexamethasone in patients with primary hemophagocytic lymphohistiocytosis.

METHODS

STUDY DESIGN AND OVERSIGHT

NI-0501-04 is a phase 2–3, open-label, single-group study performed at 14 sites in Germany, Italy, Spain, the United Kingdom, and the United States. The study consisted of screening, an 8-week treatment period (shortened to 4 weeks if donor availability and the patient's condition allowed hematopoietic stem-cell transplantation), and a short-term 4-week follow-up. In a long-term study (NI-0501-05) in which treatment continued, if needed, as a bridge to transplantation, we collected follow-up data until 12 months after transplantation (see Fig. S1 in the Supplementary Appendix and the study protocol, both available with the full text of this article at NEJM.org). Results of the combined analysis of the NI-0501-04 and NI-0501-05 studies at the regulatory cutoff date are presented here.

Approval was obtained from an institutional review board or an independent ethics committee at each center. Written informed consent was provided by the patients' legal representatives. The study was designed by the scientific steering committee and the sponsor (NovImmune). The sponsor was responsible for data gathering and management, statistical analysis, and reporting of the results. The authors drafted the manuscript with assistance from medical writers paid by the sponsor. All the authors vouch for the accuracy and completeness of the data and analyses and for the fidelity of the study to the protocol.

PATIENTS

Previously treated patients and previously untreated male and female patients who were 18 years of age or younger and who had primary hemophagocytic lymphohistiocytosis were included. All the patients had active disease at enrollment, and the patients who had received previous treatment had worsened or reactivated disease, had had an unsatisfactory response to

conventional therapy, or were unable to continue to receive conventional therapy because of adverse effects. Primary hemophagocytic lymphohistiocytosis was diagnosed on the basis of molecular assessment, family history, or the presence of five or more of the eight criteria proposed by the Histiocyte Society.⁸

Eligibility criteria are summarized in Table S1. Patients with active infections that were potentially associated with interferon- γ neutralization (typical or atypical mycobacteria, *Histoplasma capsulatum*, shigella, campylobacter, leishmania, or salmonella) were excluded.

TREATMENT

The starting dose of emapalumab was 1 mg per kilogram of body weight every 3 days, and dose modifications were initially guided by clinical and pharmacokinetic assessments. Subsequently, a protocol amendment simplified dose modifications so that they relied solely on predefined clinical and laboratory criteria; after an initial dose of 1 mg per kilogram, subsequent doses could be increased to 3, 6, and up to 10 mg per kilogram (Table S2).

If the patient was not already receiving dexamethasone, it was initiated at a dose of 5 to 10 mg per square meter of body-surface area per day 1 day before the administration of emapalumab. Cyclosporine could be continued if the patient was receiving it before screening, but it could not be introduced after the initiation of emapalumab. Intrathecal therapy was allowed. After the latest protocol amendment, additional treatment for hemophagocytic lymphohistiocytosis was permitted after dose escalation of emapalumab if the treating physician considered the response to be inadequate.

OUTCOMES

The primary efficacy end point was the overall response in previously treated patients at the end of treatment in the NI-0501-04 study (Table S3 and the Statistical Analysis section in the Supplementary Appendix). The overall response included the percentage of patients with a complete response, a partial response, or an improvement in measures of hemophagocytic lymphohistiocytosis. A complete response was defined as no fever, a normal spleen size, no cytopenia, no hyperferritinemia (defined as a ferritin level

>2000 ng per milliliter), no evidence of coagulopathy, no neurologic or cerebrospinal fluid abnormalities attributable to hemophagocytic lymphohistiocytosis, and no sustained increase in the level of soluble CD25. A partial response was defined as three or more clinical and laboratory abnormalities (including central nervous system [CNS] abnormalities) associated with hemophagocytic lymphohistiocytosis that met the criteria for a complete response. Improvement in measures of hemophagocytic lymphohistiocytosis was defined as a change of greater than 50% from baseline in at least three clinical and laboratory abnormalities (including CNS involvement) associated with hemophagocytic lymphohistiocytosis if these values were not normalized.

Secondary efficacy end points (see the Statistical Analysis section in the Supplementary Appendix) included the time to response, the duration of response until the end of treatment in the NI-0501-04 study, the cumulative duration of response until conditioning (or the end of treatment if transplantation was not performed), the number of patients in whom the dose of glucocorticoids was decreased by at least 50% from the baseline dose, the number of patients proceeding to transplantation, and overall survival, including post-transplantation survival and post-transplantation event-free survival (events of interest were death, graft failure, and relapse of hemophagocytic lymphohistiocytosis).

Serum levels of C-X-C motif chemokine ligand 9 (CXCL9), an interferon- γ -induced chemokine, were measured to assess neutralization of interferon- γ (see the Supplementary Appendix). Adverse events, laboratory values, vital signs, and the development of antidrug antibodies were assessed. The protocol mandated assessment for infection (tuberculosis and Epstein-Barr virus, cytomegalovirus, and adenovirus infection) once weekly for the first 2 weeks and every 2 weeks thereafter. During emapalumab treatment, if infections were suspected, tests to assess for pathogens possibly favored by interferon- γ neutralization were required.

STATISTICAL ANALYSIS

The planned enrollment was 28 previously treated patients with data that could be evaluated. Assuming a response in 70% of the patients, the study had 90% power to show a significant im-

Characteristic	Previously Treated Patients (N=27)	Patients Who Received Emapalumab (N=34)
Age at written informed consent — yr†		
Mean	2.55±3.23	2.24±2.99
Median (range)	1.00 (0.2–13.0)	1.00 (0.1–13.0)
Sex — no. (%)		
Female	16 (59)	18 (53)
Male	11 (41)	16 (47)
Age at diagnosis of hemophagocytic lymphohistiocytosis — yr		
Mean	2.32±3.43	2.09±3.16
Median (range)	0.91 (0.03–13.81)	0.85 (0.03–13.81)
Genetic confirmation of diagnosis — no. (%)		
Gene		
<i>FHL1</i>	0	2 (6)
<i>FHL2</i>	5 (19)	7 (21)
<i>FHL3</i>	7 (26)	8 (24)
<i>FHL4</i>	1 (4)	1 (3)
<i>FHL5</i>	2 (7)	2 (6)
Griscelli's syndrome type 2	5 (19)	5 (15)
X-linked lymphoproliferative disorder		
Type 1	1 (4)	1 (3)
Type 2	1 (4)	1 (3)

* Plus-minus values are means ±SD.

† Consent was obtained from the patients' legal guardians.

provement over the null hypothesis. The analysis populations included the previously treated group (patients who had received conventional therapy before enrollment), the emapalumab group (all patients who received ≥ 1 infusion of emapalumab) (Table 1), and patients in each group with data that could be evaluated.

For the analysis of the primary end point, we used an exact binomial test at a two-sided alpha level (type I error rate) set at 5% to test the null hypothesis that the response would be 40% or less (see the Supplementary Appendix). Summary statistics with the number and percentage within each category are presented for categorical variables. Results for the evaluation of the primary end point were summarized on the basis of two-sided exact 95% confidence intervals. Kaplan–Meier curves are provided with the median time to event and two-sided

95% confidence intervals for time-to-event variables.

The duration of response was defined as the total time from the first response to loss of that response; response had to be maintained for at least 4 days to be considered in the analysis. The cumulative duration of response was assessed by adding the periods in which patients were “in response” and calculating the percentage of days “in response” over total treatment days; no response was assigned a value of 0 days.

Safety analyses were performed separately for the periods before and after conditioning. Data for patients who did not undergo transplantation by the cutoff date were analyzed as part of the preconditioning period. The association between the response and CXCL9 levels at the end of treatment was assessed by means of logistic-regression analysis.

RESULTS

STUDY POPULATION

A total of 53 patients underwent screening, and 34 patients (27 previously treated patients and 7 previously untreated patients) received emapalumab. A total of 26 patients (76%) completed the NI-0501-04 study and 8 (24%) discontinued the study prematurely. A total of 28 patients (82%) entered long-term follow-up (Fig. S2).

Patients had characteristics that were consistent with the primary hemophagocytic lymphohistiocytosis population, and early disease onset and a mutation known to cause primary hemophagocytic lymphohistiocytosis were identified in the majority of patients (79%) (Table 1). The median age at study entry was 1.0 year (range, 0.1 to 13.0), and all the signs and symptoms of hemophagocytic lymphohistiocytosis were present (Table 1 and Table S4). Previous conventional therapy included dexamethasone and etoposide in the majority of patients. During emapalumab treatment, intrathecal therapy (glucocorticoids, methotrexate, or both) was administered to 12 patients (as continuation of previous therapy in 11 patients). Five patients who were receiving cyclosporine before study entry continued to receive it. Three patients received concomitant etoposide, alemtuzumab, or both in the NI-0501-04 study. Five other patients received etoposide while they continued to receive emapalumab in the NI-0501-05 study because of an unsatisfactory response (Table S5).

EFFICACY

At the protocol-specified end of treatment (8 weeks), 63% of the previously treated patients (two-sided 95% confidence interval [CI], 42 to 81) and 65% of the patients who received emapalumab (two-sided 95% CI, 46 to 80) had had a response (Fig. 1A and Table S6). The confidence limit for the response in each group was higher than the prespecified null hypothesis of 40% ($P=0.02$ and $P=0.005$ for the comparison in the two groups, respectively). Among previously treated patients, 26% had a complete response, 30% had a partial response, and 7% had improvement in measures of hemophagocytic lymphohistiocytosis; these responses among patients who received emapalumab were 21%, 32%, and 12%, respectively (Fig. 1A). The response was

also assessed at the end of treatment independently of whether it occurred up to or after 8 weeks (the protocol-specified end of treatment) (Fig. 1B). Of the 12 patients with CNS involvement, CNS disease normalized in 6, improved in 4, and could not be evaluated in 2 because of worsening hemophagocytic lymphohistiocytosis (see the Supplementary Appendix).

During emapalumab treatment, CXCL9 levels rapidly and markedly decreased (median, 30% of the baseline level on day 5) (Fig. S5). Logistic-regression analysis indicated that low CXCL9 levels were associated with a response at the end of treatment (Fig. 1C); these findings provided support for neutralization of interferon- γ as a relevant therapeutic objective in patients with primary hemophagocytic lymphohistiocytosis.

Dexamethasone was administered at a median daily dose of 10 mg per square meter of body-surface area at baseline and tapered by at least 50% at 8 weeks in 44% of the previously treated patients and in 47% of the patients who received emapalumab. In addition, the dose of dexamethasone was reduced by 30 to 49% in 18% and 15% of the patients, respectively.

The median time to response was 8 days (95% CI, 7 to 14) in the previously treated patients and 8 days (95% CI, 5 to 10) in the patients who received emapalumab. The first response was maintained for 18 days in 75% of the previously treated patients and for 26 days in 75% of the patients who received emapalumab (Fig. S3). Four patients who received emapalumab (of whom three had been previously treated) were not included in this analysis because they did not have a response. The median cumulative durations of response to conditioning were 31.0 days and 33.5 days in the previously treated patients and the patients who received emapalumab, respectively, which represented 75.4% (interquartile range, 31 to 91) and 75.7% (interquartile range, 33 to 91) of treatment time, respectively. Figure 2A and 2B shows plots of responses in individual patients from the beginning of treatment to the initiation of conditioning.

In the previously treated group, 19 patients (70%) proceeded to hematopoietic stem-cell transplantation. A total of 47% of these patients received myeloablative conditioning, and 53% received reduced-intensity conditioning. In the emapalumab group, 22 patients (65%) proceeded

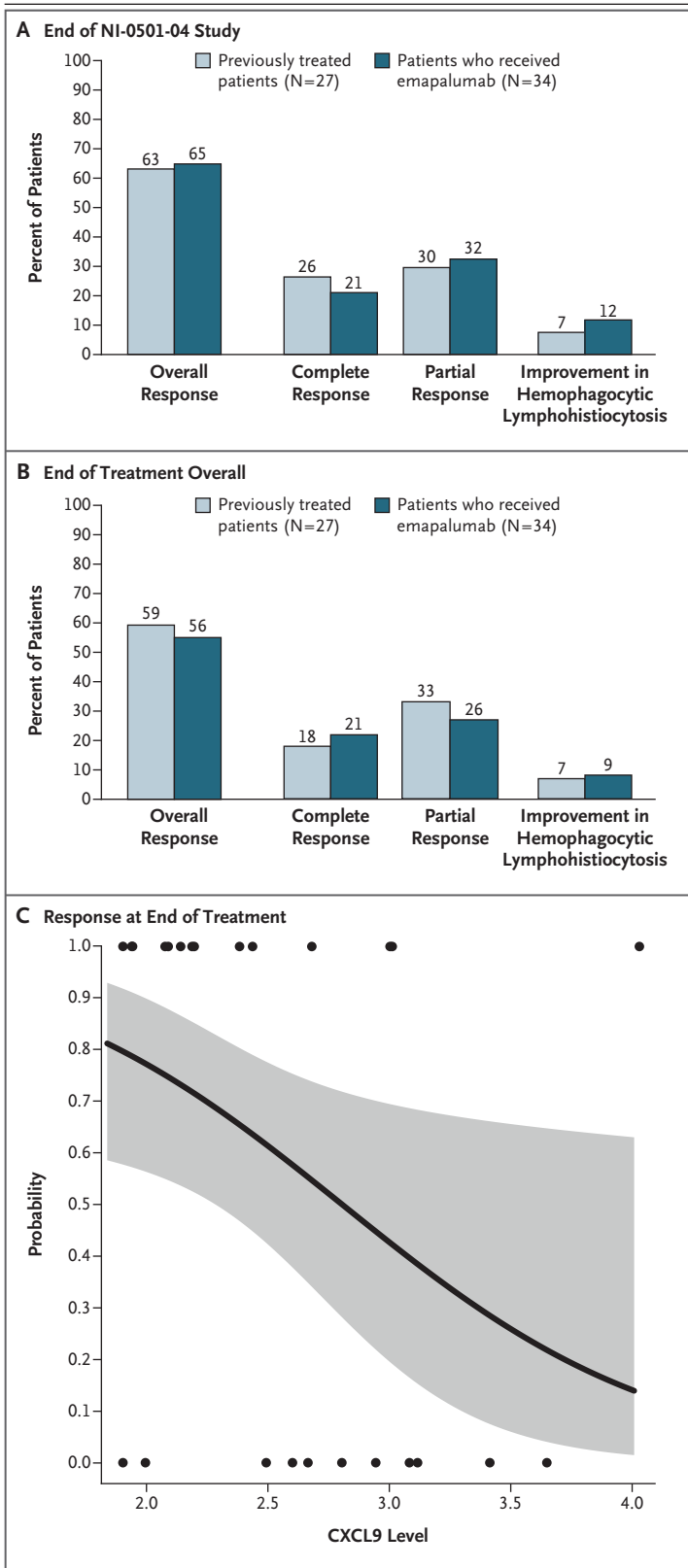


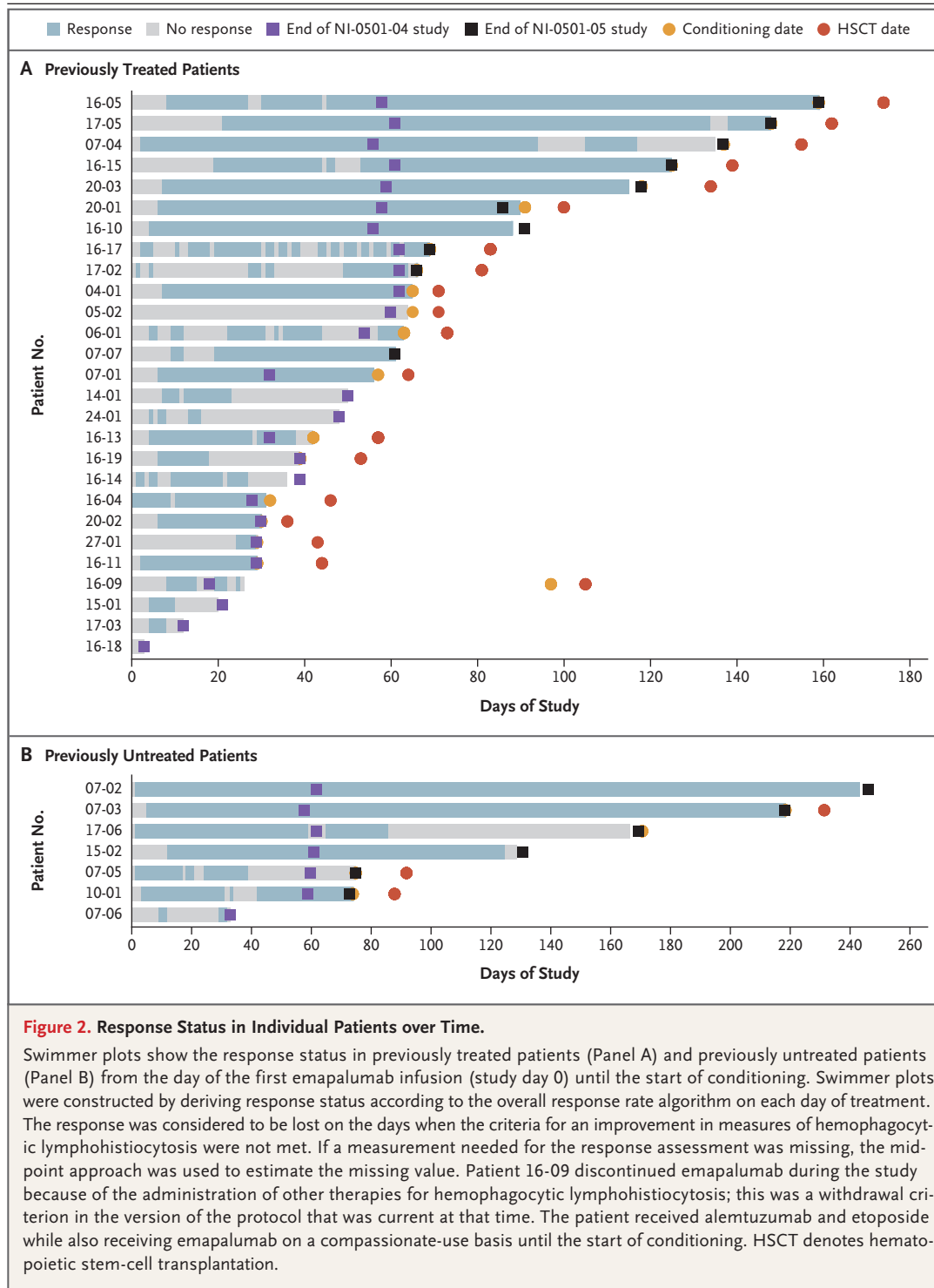
Figure 1. Percentages of Patients with an Overall Response (Complete Response, Partial Response, or Improvement in Measures of Hemophagocytic Lymphohistiocytosis).

Panel A shows the percentages of patients with a complete response, a partial response, or improvement in measures of hemophagocytic lymphohistiocytosis at the end of 8 weeks (the end of the NI-0501-04 study) among the previously treated patients and among the patients who received emapalumab. For patients who completed treatment or discontinued treatment before 8 weeks, the end of the study was 3 days after the last emapalumab infusion. Panel B shows the response among the patients at the end of treatment overall (i.e., 3 days after the last emapalumab infusion, regardless of whether it occurred before, at, or after 8 weeks [16 patients continued to receive emapalumab after 8 weeks in the long-term follow-up study]). Panel C shows the predicted probability of a clinical response at the end of treatment as a function of \log_{10} -transformed levels of C-X-C motif chemokine ligand 9 (CXCL9) at the end of treatment. The gray area indicates the pointwise 95% confidence intervals for the null hypothesis of no association, and the black dots indicate the actual observed clinical responses (on a scale from 0 to 1, with 0 indicating no response and 1 indicating a response) with the corresponding CXCL9 levels ($P=0.03$).

to transplantation (half received myeloablative conditioning, and half received reduced-intensity conditioning). Two patients had sustained control of hemophagocytic lymphohistiocytosis up to 12 months after completion of emapalumab treatment; they did not undergo transplantation because of their physicians' assessment.

Survival to transplantation and overall survival are shown in Figure 3. At the last observation, 20 of 27 patients (74%) in the previously treated group were alive with an estimated probability of survival of 73.4% (95% CI, 52.2 to 86.4) at 12 months. The corresponding values for the emapalumab group were 24 of 34 patients (71%) and 69.3% (95% CI, 50.3 to 82.2).

The estimated probability of survival after transplantation at 12 months was 89.5% (95% CI, 64.1 to 97.3) among previously treated patients and 90.2% (95% CI, 66.2 to 97.5) among patients who received emapalumab. A total of 18 patients did not have an event up to 12 months after transplantation (Fig. S4); complete donor chimerism was observed in all but 1 surviving patient at 1 year of follow-up (data were missing for 1 patient).

**SAFETY**

Safety results are presented up to the 12-month follow-up. Median durations of emapalumab administration were 48 days (range, 4 to 157) in the

previously treated patients and 59 days (range, 4 to 245) in the patients who received emapalumab.

All the patients had at least one adverse event during the preconditioning or postconditioning

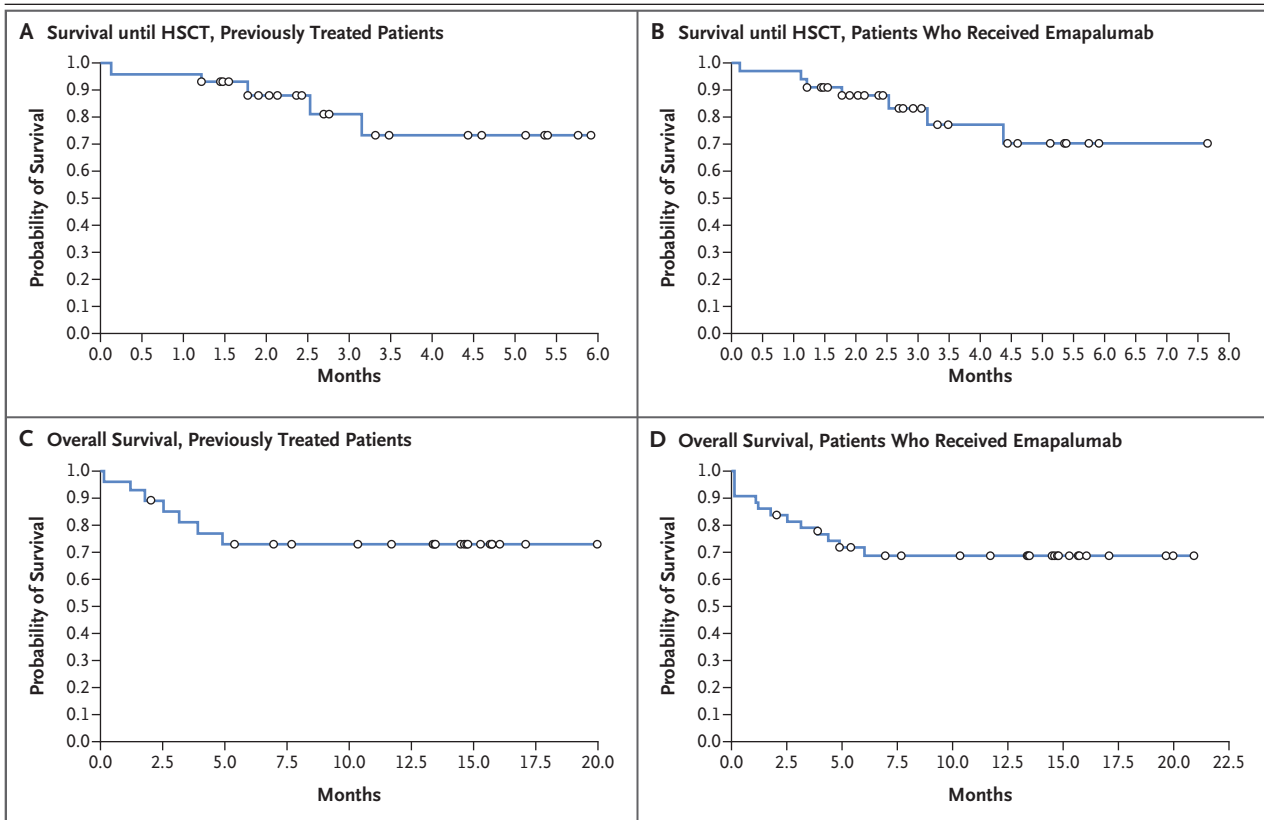


Figure 3. Kaplan–Meier Estimates of Survival.

Shown are estimates of the probability of survival until HSCT and estimates of the probability of overall survival among the previously treated patients and among patients who received emapalunab. One previously untreated patient died after HSCT after the regulatory cutoff date and was not included in the analyses. At 8 weeks, there were three deaths among the previously treated patients and one death among the previously untreated patients, all before HSCT. At 12 weeks, there were four deaths among the previously treated patients and one death among the previously untreated patients, all before HSCT. At 6 months, there were five deaths among the previously treated and two deaths among the previously untreated patients before HSCT; there were two deaths among the previously treated patients after HSCT. At 12 months, there were five deaths among the previously treated patients and three deaths (one during conditioning) among the previously untreated patients before HSCT; two of the previously treated patients died after HSCT. After HSCT, one patient died after the regulatory cutoff date.

periods (Table 2 and Table S7). Ten patients who received emapalunab died (eight before transplantation and two after transplantation) (Table S8). None of the deaths were considered by the investigators to be related to emapalunab. Causes of death included multiorgan failure (in three patients, including one with septic shock), respiratory failure (in two patients), and gastrointestinal hemorrhage, acute respiratory distress syndrome (ARDS), circulatory collapse associated with ARDS, refractory hemophagocytic lymphohistiocytosis, and neurologic deterioration (in one patient each). In addition, after transplantation and after the cutoff date, one patient died from cytomegalovirus pneumonia.

A total of 35% of the patients entered the study with either an ongoing infection or positive microbiologic tests. During emapalunab treatment and before conditioning, 13 infections were reported as serious adverse events, of which 8 were severe (Table S9). All the infections resolved except for 1 case of fatal septic shock that occurred after the second emapalunab infusion. Fifteen infections were reported as serious adverse events after conditioning, and 4 were assessed as being severe. Three infections occurred in two patients with severe complications of transplantation (graft-versus-host disease and graft failure in one patient each); both patients died. The fourth infection occurred 4 weeks after

Table 2. Adverse Events.*

Event Category	Previously Treated Patients		Patients Who Received Emapalumab	
	Before Conditioning (N=27)	After Conditioning (N=19)	Before Conditioning (N=34)	After Conditioning (N=23)
	<i>number of patients (percent)</i>			
At least one adverse event	26 (96)	19 (100)	32 (94)	23 (100)
At least one adverse event related to study drug	8 (30)	0	10 (29)	1 (4)
At least one adverse event leading to withdrawal from the study or discontinuation of the study drug	2 (7)	0	2 (6)	0
At least one serious adverse event	17 (63)	13 (68)	21 (62)	15 (65)
At least one serious adverse event related to study drug	2 (7)	0	2 (6)	0
Infection				
Reported as adverse event	16 (59)	15 (79)	19 (56)	16 (70)
At least one reported as serious adverse event	8 (30)	8 (42)	11 (32)	8 (35)
Aggravated condition†				
Reported as adverse event	12 (44)	2 (11)	17 (50)	3 (13)
At least one reported as serious adverse event	3 (11)	1 (5)	5 (15)	2 (9)
Infusion reactions				
Total	7 (26)	0	9 (26)	0
At least one reported as serious adverse event	0	0	0	0
Death				
Total	5 (19)	2 (11)	8 (24)	2 (9)
At least one serious adverse event leading to death	4 (15)‡	2 (11)	7 (21)‡	2 (9)

* The period before conditioning refers to the time between the initiation of emapalumab treatment and the day before the initiation of the conditioning regimen. The period after conditioning refers to the time between the initiation of conditioning and the last available observation.

† An aggravated condition is a reactivation, flare, or worsening of hemophagocytic lymphohistiocytosis. Twenty-five such events occurred in 17 patients who received emapalumab: 21 resolved, 1 improved, and 3 did not resolve. Among these 3 patients, 1 patient who received etoposide, alemtuzumab, and antithymocyte globulin had an aggravated condition that did not resolve, 1 patient who received one dose of alemtuzumab and one dose of etoposide had an aggravated condition that did not resolve, and 1 patient transferred to palliative care because of a preexisting neurologic coexisting condition and acute neurologic deterioration.

‡ One patient died after withdrawal of treatment; this patient was not reported to have an event with a fatal outcome.

transplantation and resolved. One case of disseminated histoplasmosis and one case of necrotizing fasciitis were reported by the investigators as being related to emapalumab.

No clinically significant changes noted in hematologic findings, clinical laboratory values, hepatic or renal function, urinalysis results, or vital signs were attributed by the investigators to emapalumab. Signs of myelosuppression related to emapalumab did not develop in any of the patients. The adverse-event profile was not ap-

preciably different in patients who received additional treatment for hemophagocytic lymphohistiocytosis and in those who received emapalumab only, probably because of the small sample size and the few and often reduced doses of the additional treatments for hemophagocytic lymphohistiocytosis.

Antidrug antibodies were detected in one patient. No related adverse events (in particular, no hypersensitivity reaction) occurred when the antibodies were detected, and the pharma-

cokinetic properties of emapalumab were unchanged.

DISCUSSION

In this study, neutralizing interferon- γ and controlling hyperinflammation with emapalumab were efficacious in previously treated children with primary hemophagocytic lymphohistiocytosis. Most patients carried mutations known to cause hemophagocytic lymphohistiocytosis and were in poor health, and conventional therapy for hemophagocytic lymphohistiocytosis had failed to control the disease. In the studies conducted by the Histiocyte Society involving newly diagnosed patients with primary hemophagocytic lymphohistiocytosis (HLH-94 and HLH-2004),^{5,6} the percentages of patients with a response at 2 months, as subjectively assessed by treating physicians, were 59% and 51%, respectively. In our study, the percentage of previously treated patients with a response, as assessed by objective clinical and laboratory criteria, was 63%. Only seven previously untreated patients received emapalumab; more patients must be evaluated before conclusions can be drawn about the efficacy of emapalumab in this group.

During emapalumab treatment, improvement in measures of hemophagocytic lymphohistiocytosis followed the same temporal pattern as the decrease in serum levels of CXCL9, a chemokine exclusively induced by interferon- γ ²² and hence a measure of interferon- γ neutralization. Logistic-regression analysis indicated an association between the probability of a response and a decrease in the CXCL9 level at 8 weeks; this suggests that neutralization of interferon- γ is a relevant therapeutic objective in primary hemophagocytic lymphohistiocytosis.

Primary hemophagocytic lymphohistiocytosis is a highly unstable disease with frequent reactivations. In this study, frequent assessment of disease measures allowed determination of the time during which patients had a response until conditioning (or 8 weeks for patients who did not undergo transplantation). The median cumulative duration of response was 75% of days until transplantation. The frequent dosing (relative to other monoclonal antibodies) and dose adjustment based on clinical and laboratory values may have led to an increase in the duration of response.

Patients with primary hemophagocytic lymphohistiocytosis are quite ill, with a variety of disease manifestations. Emapalumab did not appear to amplify the adverse events associated with the disease. Most adverse events were mild and attributable to reactivation or worsening of hemophagocytic lymphohistiocytosis, coexisting conditions, toxic effects of coadministered drugs, or all of these variables. With the exclusion of infusion-related reactions, only two serious adverse events related to emapalumab were reported; data to confirm this initial favorable profile are lacking. No reductions in the dose of emapalumab were implemented. Treatment was discontinued in one patient with disseminated histoplasmosis. No premedication was required for emapalumab infusions. The patients who received emapalumab did not have myelosuppression, which is typically observed with conventional etoposide-based therapy and, together with organ toxicity, results in frequent dose reductions and discontinuations.⁶ The administration of emapalumab permitted dexamethasone tapering.

As expected in this population,^{2,5,6} one third of the patients had an infection at the beginning of the study. Infections also occurred frequently during the study and were usually associated with disease flares. Infectious episodes resolved with antimicrobial therapy within the expected time period. The absence of interferon- γ biologic activity might lead to increased susceptibility to specific infections.²³⁻²⁶

Most patients who received emapalumab in our study proceeded to allogeneic hematopoietic stem-cell transplantation. The outcomes in patients who underwent transplantation compared favorably with those reported previously with either myeloablative or reduced-intensity conditioning regimens.^{27,28} This may be related to the ability to decrease doses of glucocorticoids and prevent toxic effects associated with conventional therapies for hemophagocytic lymphohistiocytosis. Two patients (without a confirmed genetic diagnosis) did not have an HLA-compatible donor and did not undergo transplantation by the end of the study follow-up period; hemophagocytic lymphohistiocytosis resolved in these patients, and they survived.

The use of additional therapies for hemophagocytic lymphohistiocytosis was allowed in patients who had an insufficient response to emapalumab, given the dismal prognosis in young patients in

whom multiple lines of therapy fail. No safety concerns were raised because of concomitant administration of therapies. Although a clinically meaningful improvement in disease control was not observed in the limited number of patients who received additional treatments, the addition of conventional agents to emapalumab remains an option in patients with hemophagocytic lymphohistiocytosis that is difficult to treat, and it may permit the use of lower doses of conventional agents, shorter durations of treatment with these agents, or both.

In conclusion, in this study, emapalumab was effective with a low level of toxic effects in patients with primary hemophagocytic lymphohistiocytosis. The study provides support for further investigation of emapalumab in patients with

secondary forms of hemophagocytic lymphohistiocytosis in whom interferon- γ has been suggested to be pathogenic.¹⁴

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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APPENDIX

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