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An observational, multicenter study to evaluate interferon gamma (IFNγ) and other inflammatory mediators in patients with malignancy-associated hemophagocytic lymphohistiocytosis (M-HLH)

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Confidentiality Agreement

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Contents

Background and Rationale

Interferon gamma (IFNγ) in secondary HLH

HLH is a syndrome of severe immune activation and deregulation characterized by hyperactive macrophages and lymphocytes, pro-inflammatory cytokine hypersecretion, hemophagocytosis, and tissue and organs damage. HLH occurs as either a primary (pHLH, familial) or secondary (sHLH, sporadic) disorder (Henter et al., 1998; Janka, 1983). pHLH is an autosomal recessive disease with an incidence of 1/50,000 live-born children (Henter et al. 1991; Arico et al. 1996). Patients often have a clear familial inheritance or genetic mutation. pHLH is caused by homozygous mutations in the genes coding for perforin, Munc13-4, syntaxin 11, Munc18-2 and other proteins involved in cytotoxic granule activation, polarization, priming, fusion, or function (Jordan et al., 2011; Zhang et al., 2014). These mutations result in defective immune effector cell function, uncontrolled activation of histiocytes, and pathognomic clinical manifestations of HLH. Secondary HLH often occurs as a result of pathological immune activation in response to a trigger. Frequently noted triggers include malignancies (especially hematological malignancies including acute leukemia's and lymphomas), infections (especially EBV) and rheumatologic disorders (sJIA, SLE). The list of triggers associated with secondary HLH is extensive (Henter et al., 1997). Primary HLH is reported to be more frequent in childhood.

The pathogenesis of secondary HLH remains a matter of debate. Reports have recently described patients developing Macrophage Activation Syndrome (MAS) in the context of systemic juvenile idiopathic arthritis (sJIA). These patients were identified to be heterozygous for rare variants in the primary HLH-associated genes (Zhang et al., 2014) highlighting potential etiological, clinical, and pathological similarities between familial and acquired forms of HLH. A link between mutations in the perforin gene and predisposition to hematological malignancies has been described (Clementi et al., 2005; Zhang et al., 2014), further supporting a possible contribution of hypomorphic mutations in HLH-related genes to the development of M-HLH (Lehmberg 2015).

Immune-activation and immune mediated pathology likely play a central role in the evolution of HLH. Secondary HLH is characterized by acute clinical signs and symptoms of immune activation including hepatomegaly, jaundice, adenopathy, rash, seizures, and focal neurologic

deficits as well as laboratory measures such as strikingly high serum levels of numerous cytokines including interferon gamma (IFNγ), tumor necrosis factor α (TNF-α), interleukin 6 (IL-6), IL-10, and macrophage–colony-stimulating factor (M-CSF) (Akashi et al., 1994; Ohga et al., 1993). Furthermore, biopsies of lymphoid tissues or histological examination of liver tissue from HLH patients reveal highly activated macrophages and lymphocytes, further supporting striking activation of the immune system. Secondary HLH carries a significant mortality rate with approximately 10 to 30% of the diagnosed patients succumbing from the disease (Celkan et al., 2009; Minoia et al., 2014; Grom et al., submitted). Categorizing patients into primary or secondary HLH based on clinical manifestations is often difficult and may be of limited value. Treatment should be initiated expediently if the diagnosis of HLH is suspected, regardless of the classification/trigger.

Secondary HLH that develops in the setting of malignancy is also known as malignancy-associated hemophagocytic lymphohistiocytosis (M-HLH). The majority of malignancies triggering secondary HLH in children and adults are lymphomas and leukemia. While primary forms of HLH are more common in younger patients, M-HLH is more frequent in adults (Ramos-Casals et al., 2014). Machaczka et al. (2011) estimated that HLH affects 0.9% of adults with hematological cancer, but the prevalence may be as high as 20% in patients with specific types of B-cell lymphoma's (intravascular B-cell lymphoma or B-cell lymphoma without peripheral adenopathies) and T-cell lymphoma (nasal natural-killer-cell or panniculitis-like subtypes) (Ramos-Casals et al., 2014).

M-HLH may manifest during the treatment (iatrogenic) of a known malignancy or as the presenting feature of a yet undiagnosed malignancy (non-iatrogenic). It is postulated that the hyperinflammation is triggered by the neoplasm or its treatment, due to an excessive secretion of pro-inflammatory cytokines by the malignant cells or by T-cell activating immunotherapies for the treatment of leukemia/lymphoma and emerging for treatment of solid tumors (e.g. bispecific monoclonal antibody blinatumomab, CAR T-cell therapies) (Hijiya et al., 2005; Teachey et al., 2013; Lee et al., 2014).

The malignancy induced immunodeficiency combined with therapy likely predisposes to infections and defective T-/NK-cell function reducing the threshold for triggering HLH in these

patients (Celkan et al., 2009). Indeed, similarly to primary HLH, infections are often identified as co-triggers in iatrogenic M-HLH.

The clinical course of M-HLH is often aggressive, and characterized by poor outcome, which are further impacted by the nature and status of the underlying malignancy. A single center retrospective study in adults reported only 1 of 8 patients survived despite identification of HLH and implementation of HLH directed therapies (Machaczka et al., 2011). A recent retrospective study in children and adolescents (n=27) reported a 6-month survival rate of 67% in non-iatrogenic M-HLH and 63% in iatrogenic M-HLH (Lehmberg et al., 2015). The group at MD Anderson Cancer Center retrospectively identified pathologic hemophagocytosis and/or lymphohistiocytosis in 61 adult patients with underling malignancies between 1991-2001. Thrity five patients had additional systemic variables conferring a high suspicion for M-HLH. The median survival among the 35 patients was a dismal 1.5 months. The median survival was 1.2 months among patients treated with HLH directed therapy as compared to 1.8 months among those not treated with HLH directed therapies. 31% of patients were alive at 6-months (Tamamyam, Daver et al.; manuscript submitted).

An effective therapeutic approach to M-HLH (iatrogenic and non-iatrogenic) remains unknown. Of note is that agents that are currently considered as standard therapies for HLH (corticosteroids, etoposide) are often part of the treatment of malignancies known to be able to cause M-HLH. Furthermore, the addition of etoposide, alemtuzumab, dexamethasone may induce worsening myelosuppression and immunodeficiency in patients who have an underlying malignancy and/or recent systemic therapy. A non-myelosuppressive and less immunosuppressive therapy would be an ideal approach to evaluate in M-HLH patients. A prompt initiation of an HLH-directed regimen (before or in combination with the malignancy-directed therapy) is of critical importance to decrease the high mortality rate in these patients. Furthermore, studies have described the use of tocilizumab, an anti-IL-6R antibody, to manage cytokine release syndrome occurring after treatment with T-cell engaging therapies (Barrett et al., 2014).

NI-0501 is a fully human anti-interferon gamma (IFNγ) monoclonal antibody (mAb) that binds to and neutralizes IFNγ. NovImmune is developing NI-0501 as the first targeted monoclonal therapy for HLH. Several lines of evidence support the investigation and use of therapeutic agents targeting IFNγ in HLH:

1. Two animal models of pHLH and two animal models of sHLH have been investigated in the context of the NI-0501:

   - Perforin knockout mice and Rab27-deficient mice develop all the diagnostic and many of the clinical and laboratory characteristics of human primary HLH when infected with lymphocytic choriomeningitis virus (LCMV) as a trigger. Neutralization of the high circulating IFNγ levels in both animal models led to the reversal of HLH clinical and laboratory abnormalities, and dramatically improved survival in the animal model characterized by high mortality (pfp -/- mice) (Pachalopnik Schmid et al., 2009, Jordan et al., 2004).

   - Repeated administration of CpG, causing TLR9 stimulation, has been used to mimic a chronic severe hyperstimulation in healthy mice as a model of HLH secondary to infection. Although these mice do not necessarily die, they develop typical clinical and laboratory features of HLH (Behrens et al., 2011). Administration of an anti-IFNγ antibody led to reversal of clinical and laboratory features of HLH. Importantly, in this model it was demonstrated that administration of the anti-IFNγ antibody also led to full neutralization of IFNγ effects in relevant target tissues, such as liver and spleen (Buatois et al, submitted).

   - To study the physiopathology of sHLH in the context of rheumatic diseases, an animal model has been generated using IL-6 transgenic mice expressing high levels of IL-6, to mimic what occurs in patients with sJIA. When triggered with TLR ligands, these mice die with many of the features of the human HLH (Stippoli et al. 2012). In these mice, when IFNγ was neutralized by administration of an anti-IFNγ antibody, survival was markedly improved and HLH laboratory parameters reverted.

   In conclusion, in all presented animal experiments, IFNγ was demonstrated to be a key pathological effector in disease onset and progression.

2. Primary and secondary HLH patients have hypercytokinemia with elevated levels of several pro-inflammatory cytokines including IFNγ (Henter et al., 1991; Janka et al., 1998; Xu et al. 2012). More recently, high levels of IFNγ were demonstrated both in patients with HLH secondary to infections and in sJIA patient developing MAS (Buatois et al., manuscript

submitted; Bracaglia et al. manuscript submitted). The levels of CXCL9, CXCL10 and CXCL11, three chemokines known to be induced by IFNγ, were also significantly elevated. Noteworthy, levels of IFNγ and of the three IFNγ-inducible chemokines were found to significantly correlate with laboratory parameters of disease severity, such as ferritin, platelet count and transaminases.

3. A Phase 2 pilot study is presently ongoing to evaluate the efficacy and safety of treatment with NI-0501, an anti-IFNγ monoclonal antibody, in pHLH. Based on data gathered so far, NI-0501 treatment has been well tolerated and shown a favorable impact on all relevant clinical and laboratory features of HLH such as fever, splenomegaly, cytopenia, hyperferritinemia, hypofibrinogenemia, and also CNS signs/symptoms (Jordan et al, 2015).

No animal models specific to M-HLH have been described (Brisse et al., 2015). The levels of IFNγ and other pro-inflammatory cytokines at diagnosis and their correlation with clinical evolution and severity of the HLH manifestations during and after therapy have been poorly characterized for M-HLH. The fact that primary HLH and HLH secondary to inflammatory/autoimmune diseases or infections have many pathophysiological and clinical features in common with M-HLH, suggests that IFNγ might also play a key role in M-HLH. The present observational study is designed to provide a better understanding of the potential use of IFNγ and IFNγ-inducible chemokines as markers of M-HLH disease activity and potential prognosis and of the possible role of IFNγ as a therapeutic target in M-HLH, and to explore the genetic profiles in patients with M-HLH with regard to HLH-related genes.

Study Objectives:	• To determine the levels of inflammatory markers including, but not limited to interferon gamma (IFNγ), interleukin 1 beta (IL-1β), interleukin 6 (IL-6), interleukin 10 (IL-10), interleukin 17 (IL-17), soluble IL-2 Receptor α (sCD25), C-X-C chemokine ligand 9 (CXCL9), C-X-C chemokine ligand 10 (CXCL10), C-X-C chemokine ligand 11 (CXCL11), soluble CD163 (sCD163), neopterin and Tumor Necrosis Factor alpha (TNFα) in patients diagnosed with M-HLH and whenever possible, to monitor the evolution over time of these markers. • To assess the relationship between the above mentioned inflammatory cytokines and disease activity. • To assess the relationship between genetic variants of the genes typically causing primary HLH and M-HLH and associated inflammatory markers.
Sample Size:	A minimum of 14 (maximum of 50) M-HLH patients will be studied, including a minimum of 7 non iatrogenic M-HLH and 7 iatrogenic M-HLH. A control group of 10 patients with a diagnosis of hematological malignancy in absence of HLH will also be evaluated.
Study Population:	Male and female (adult and children) patients who are diagnosed with M-HLH and that meet the inclusion criteria listed below. In addition, patients with a diagnosis of hematological malignancy in the absence of HLH will be included as a control group.
Inclusion Criteria:	1. Patients diagnosed with HLH in the context of a malignancy. The diagnosis of M-HLH will be established by the treating physician. 2. The patient or patient's legal representative (in case the patient is < 18 years old) must have consented to the use of their clinical data for research purposes at the site. 3. For the control group, patients with a diagnosis of hematological malignancy and never diagnosed with HLH or no suspicion of HLH (at any time, including time after sample collection in case of use of retrospective sample).
Study Design:	This is a non-interventional study designed to determine the levels of pro-inflammatory markers (as listed above) in patients diagnosed with M-HLH and to assess the relationship between the biomarkers

	and disease activity and prognosis during the M-HLH course. Inflammatory markers will also be measured in a group of control patients diagnosed with hematological malignancy in absence of HLH (as described above). Data collection may be performed retrospectively if sufficient clinical information is available to allow for a meaningful interpretation of the biomarker results. An approximate volume of 500 µl – 1 ml of serum or plasma is required per time point. Whenever possible, serum (and not plasma) should be collected, as this is the preferred matrix for the biomarker analysis. In addition to the serum samples for the biomarker analysis, relevant information gathered by the treating physician will be collected in a data collection form. This will include information on the clinical presentation of M-HLH, the type of underlying malignancy, the date of onset of malignancy in relation to HLH manifestations, treatment regimen prior to and/or ongoing at the time of M-HLH onset, laboratory parameters, M-HLH disease activity (e.g. newly diagnosed, reactivation), specific HLH therapy with best response to the therapy, other concomitant medications, patient follow-up and disposition, stem cell transplant status, duration of response, and survival. Whenever possible, collection of serum samples for biomarker analysis and relevant information should occur at M-HLH diagnosis, at regular time intervals during the treatment course, at resolution and/or reactivation of the disease. In addition to the above a minimum of 1 ml of whole blood will be collected (EDTA tubes) for genetic characterization and identification of the presence of genetic variants of the genes typically causing primary HLH. A specific consent for genetic testing must be given by the patient. Genetic samples may also be collected from existing bank of samples (frozen whole blood in EDTA or frozen extracted DNA), if proper consent has been obtained.
Study Duration:	This study collects information on M-HLH patients at diagnosis and during treatment of the disease, and will last until a minimum of 14 (maximum of 50), including at least 7 iatrogenic and 7 non-iatrogenic M-HLH patients and up to 10 hematological malignancy patients in absence of HLH have been recruited.
Exploratory Parameters:	**1. Laboratory parameters,** at the time of sample collection, assessed at the local laboratory, according to local clinical practice, such as:

- Hemoglobin, Hematocrit, Red blood cells, white blood cells and differential count, platelets
- Fibrinogen
- Ferritin
- Fasting triglycerides
- AST, ALT, Alkaline Phosphatase
- BUN, serum creatinine
- Albumin (if available)
- Sodium (if available)
- Beta2 microglobulin (if available)
- Serum IgG levels (if available)
- Lactate dehydrogenase
- Total and conjugated Bilirubin
- D-dimers
- CRP
- NK-cell activity (if available)

2. **Inflammatory markers of disease activity.** The following assessments will be performed by the NovImmune Bioanalytical Assay Laboratory:
   - IFNγ
   - sCD25
   - IL-1β, IL-6, IL-10, IL-17
   - TNFα
   - CXCL9, CXCL10, CXCL11
   - sCD163 and neopterin
3. **Additional parameters recorded at the time of diagnosis** will be collected when available for *a posteriori* diagnosis:
   - Temperature
   - Splenomegaly
   - Hb concentration
   - Platelet and neutrophils count
   - Triglycerides

	• Fibrinogen • Hemophacocytosis • NK cell activity • Ferritin • sCD25
Statistical Analysis:	All analyses are exploratory. Statistical analyses of the data collected in this study will be focused on providing tabular and graphical summaries of the levels of inflammatory markers and of the clinical features of the disease both at diagnosis and during the course of treatment. Levels of inflammatory markers will be compared between patients with active M-HLH and the control group (i.e. hematological malignancy in absence of HLH). In addition, the degree of correlation between inflammatory markers, and between inflammatory markers and the severity of clinical manifestations, response to therapy, and survival of the patients will be assessed. Analyses may also be performed to study these relationships in various subgroups of patients, depending on the demographic, genetic and clinical characteristics observed, including *a posteriori* diagnosis based on HLH-2004 diagnostic criteria (Henter et al., 2007). Criteria for diagnosis are: i) Fever ii) Splenomegaly iii) Cytopenia (affecting ≥ 2 of 3 lineages in peripheral blood): • Hb <90 g/L (in infants < 4weeks: Hb<100 g/L) • Platelets<100 x 10^9/L • Neutrophils <1.0 x 10^9/L iv) Hypertriglyceridemia and/or hypofibrinogenemia: Fasting triglycerides ≥3.0 mmol/L; Fibrinogen ≤1.5 g/L v) Hemophagocytosis in bone marrow or other specimens vi) Low or absence NK-cell activity (according to local laboratory reference) vii) Ferritin ≥ 500 µg/L viii) sCD25 ≥ 2400U/ml
Medications:	Any medications that are considered necessary for the patient's welfare are given based on the decision of the treating physician.
Informed consent:	It is the responsibility of the investigator to obtain written informed consent from each patient participating in this study, after adequate explanation of the aims, methods and potential hazards of the study. An informed consent form will be signed. An additional signature

	will be requested specifically for genetic analyses. Patients may withdraw their consent at any time; it is the responsibility of the investigator to contact the sponsor for specific patient withdrawal of consent while maintaining the confidentiality by communicating only patient codes. The sponsor will proceed with the destruction of all left over patient material within 30 days. The sponsor will also inform and request confirmation from potential collaborators to destroy aliquots that may have been transferred under collaboration agreements for the purpose of the research described in this protocol. The data generated prior withdrawal of consent will be maintained.
Data collection and patient confidentiality:	Relevant clinical information including date of diagnosis, medical history and previous and current treatments will be gathered by the treating physician. The investigator must assure that patients' anonymity will be maintained and that their identities are protected from unauthorized parties. On Data Collection Forms or other documents or material submitted to the sponsor, patients should not be identified by their names, but by an identification code. The investigator should keep a patient log showing codes, names and addresses. The investigator should maintain documents not for submission to NovImmune, e.g., patients' written consent forms, in strict confidence.
Study administration:	**Record Retention** The investigator will ensure that essential records are kept in a secure archiving facility for the retention period stipulated in the study contract. Essential documents include, but are not limited to, the following: • Signed informed consent documents for all patients • Subject identification codes • Record of all communications between the investigator and the IEC • Composition of the IEC • Record of communications between the investigator, NovImmune and their authorised representative These records will be held in the Investigator's archives. If the Investigator is unable to meet this obligation, the Investigator must ask NovImmune for permission to make alternative arrangements.

Details of these arrangements should be documented in the clinical study centre TMF.

Financial Disclosure

Investigator is required to provide financial disclosure information to allow NovImmune to submit complete and accurate certification or disclosure statements in accordance with applicable national and local regulations upon request. In addition, investigator must provide NovImmune with a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Disclosure of Protocol and Study Results and Publication Policy

Publication or communication of results will be decided upon completion of the study or earlier if data are considered sufficiently novel and robust. NovImmune will comply with the requirements for publication of results involving human research.

Authorship will be determined by mutual agreement and in line with ICMJE authorship requirements. Any formal publication of the study in which contribution of NovImmune personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate NovImmune personnel.

So-called 'ghost writing' is not permitted. All contributors who do not meet the criteria for authorship should be listed in an acknowledgments section. Examples of those who might be acknowledged include a person who provided purely technical help, writing assistance, or a department chairperson who provided only general support.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of NovImmune, except where agreed otherwise.

Monitoring and Auditing

As the aim of this study is mainly to test blood for research purpose no specific monitoring at site is foreseen by NovImmune. However for compliance with applicable government regulations with respect to current GCP and standard operating procedures, direct access to the on-site study documentation and medical records must be ensured to any audit or inspections.

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