HIGHLY ELEVATED FERRITIN LEVELS ARE ASSOCIATED WITH HAEMOPHAGOCYTIC LYMPHOPHISTIOCYTOSIS/MACROPHAGE ACTIVATION SYNDROME – ARE WE MISSING TREATABLE DIAGNOSES? A RETROSPECTIVE SERVICE EVALUATION OF DIAGNOSIS IN PATIENTS WITH FERRITIN >10,000 MICROGRAM/L

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Background: Haemophagocytic lymphohistiocytosis (HLH)/macrophage activation syndrome (MAS) is a hyperinflammatory syndrome potentially leading to critical illness. Early treatment reduces mortality but diagnosis requires a high index of suspicion. Highly elevated ferritin levels (HEF) >10,000 μg/L are highly specific for HLH/MAS [1] and should prompt consideration of hyperinflammation. Diagnostic guidelines for HLH requiring the presence of >5/8 criteria [2], and classification criteria for MAS complicating systemic juvenile idiopathic arthritis (sJIA) have been published [3].

Objectives: To assess recognition of HLH/MAS in a paediatric population with HEF.

Methods: This retrospective study was conducted at 11 centres under local service evaluation permissions. Biochemistry databases identified patients ≤16 years with serum ferritin >10,000 μg/L during a 3-year period. Each case was assessed against the 2004 HLH criteria and, for patients with sJIA, the 2016 MAS criteria. Due to limited access to some of the laboratory tests, previously-published modified HLH criteria using a threshold of >4/5 (excluding tissue haemophagocytosis, decreased natural killer cell function, increased soluble interleukin-2 receptor) were also applied to all patients [4].

Results: 153 patients (55.6% male) were identified. Patient diagnoses included: infections (29.4%), rheumatological (17.0%) and malignancies (17.0%). A diagnosis of HLH/MAS was made by the treating clinical team in 39.9%, and considered in a further 16.3%. Using all available data, 30/153 (19.6%) met >5/8 criteria and 93.3% of these patients were diagnosed with HLH/MAS by the treating team. 56 (36.6%) met >4/5 criteria and 33 (58.6%) of these were diagnosed with HLH/MAS by clinicians. HLH/MAS was not documented as being considered in the differential in 23.2%. Of 23 patients with sJIA, 82.6% met MAS classification criteria and 49.5% of these were diagnosed with MAS by the treating clinicians. Overall mortality was 32.7% (50/153) and was 27.9% (17/61) in patients diagnosed with HLH/MAS during their admission.

Conclusion: Although HEF is highly specific for HLH/MAS, the diagnosis was only made or considered in just over half of paediatric patients with this laboratory result. Increased awareness of this potentially-lethal condition is likely to lead to earlier treatment and reduced mortality.

REFERENCES:

Disclosure of Interests: Ethan Sen: None declared, Beverley Almeida: None declared, Louise Moran: None declared, Charlene Foley: None declared, Najla Abdelrahman: None declared, Rosie Close: None declared, Ema-Louise Long: None declared, Joshua Bennett: None declared, Jason Palman: None declared, Cathrina Anderson: None declared, Kirsty McErlane: None declared, Samantha Deepak: None declared, Kathy Gallagher: None declared, Peter Bale: None declared, Kamran Mahmood: None declared, Clare Pain: None declared, Flora McErlane: None declared, Athimalapet Ramanan Consultant for: AbbVie, UCB, Sobi, Eli Lilly, Rachel Tattersall: None declared.


CLINICAL PRESENTATION, GENETIC ANALYSIS AND IFN-SCORE IN PATIENTS WITH UNDEFINED INTERFERONOPATHIES

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Background: In the last years, an expanding group of complex genetic disorders characterized by disturbance of the homeostatic control of IFN-mediated immune responses, have been identified, so called type I interferonopathies. An increased expression of type I IFN regulated genes, IFN signature (IS), is described in these conditions. IS represent a useful tool in clinical practice to classify patients with suspected interferonopathies.

Objectives: To evaluate the correlation between clinical presentation, genetic analysis and IFN-score in 10 patients with undefined interferonopathies.

Methods: Patients with suspected interferonopathy based on the presence of typical clinical manifestations (neurological, musculo-cutaneous symptoms), laboratory parameters (complement deficiency, low platelet count, presence of autoimmunity), instrumental abnormalities (cerebral calcification), were screened for the IFN-score. Defined IFN-mediated diseases were excluded. Patients presenting with a high IFN-score value (above a fixed cut-off of 10) underwent genetic screening by running a panel of 24 genes known to be involved in interferonopathies.

Results: 10 patients with suspected interferonopathy followed in a single pediatric rheumatology center were included. 7/10 presented with recurrent episodes of fever (table). Patient 2, 3 and 7 displayed neurological manifestation, respectively epilepsy, epilepsy and mental retardation and progressive hemiplegia. To note epilepsy in patient 2 might be correlated to a bilateral intraventricular hemorrhage presented at birth. In two patients (1,4) gastrointestinal manifestation resembling inflammatory bowel diseases were described while patients 5, 7 and 10 suffered from recurrent abdominal pain, diarrhea and patient 10 from hypertransaminasemia. Half of the patients complained arthralgia; arthritis developed in patient 2. Cutaneous involvement presented in 3 patients (1,3,6) respectively with a widespread panniculitis of trunk and limbs, aspecific vasculitis and Schonlein Henoch purpura. Other cutaneous manifestation were urticarial rash (pt 2) and an erythematous, desquamative confluent eczema (pt 4). Autoimmunity was confirmed in 2/10 patients. Two patients (4, 8) had an immunological defect with recurrent infections. The genetic analysis resulted negative in patients 1 and 7 and is still ongoing in patients 5, 6 and 8. Patients 2,3,4,9 and 10 carried one mutation in at least one IFN-correlated gene not confirming the diagnosis. All patients presented an increased IS ranging from 14.2 to 172.5.

Conclusion: An elevated IFN-score represent a useful instrument in the clinical practice to classify patients with suspected interferonopathy. It may represent an important tool to select those patients to be genetically screened with a defined panel of interferonopathies correlated genes. In those patients in which the genetic analysis result negative, the presence
FRIO543 Efficacy and Safety of Intravenous Golimumab in Patients with Juvenile Idiopathic Arthritis: Results from a Phase 3 Open-Label Study

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Objectives: To assess efficacy & safety of intravenous golimumab in pediatric patients with active polyarticular course juvenile idiopathic arthritis despite methotrexate therapy through 28 weeks of treatment.

Methods: A multicenter, Phase 3, single arm, open-label trial was conducted using intravenous golimumab at a dose of 80 mg/m^2 given at weeks 0 & 4, then every 8 weeks thereafter, in pediatric patients ages 2-17 years old with active polyarticular course juvenile idiopathic arthritis despite methotrexate therapy. Patients received commercial MTX weekly at same BSA-based dose as at time of study entry. All the results below are based on full analysis set which includes all patients who received at least 1 dose of study agent.

Results: 180 patients were screened (130 enrolled, 127 treated) with the first patient screened on 22Dec2014; last patient first treated 26Dec2017, & last patient’s Wk28 visit was 09Jul2018. Proportion of JIA ACR 50, 70, & 90 responders at Wk28 was 83.5%, 79.5%, 70.1%, & 46.5%, respectively. 29.1% of patients met criteria for inactive disease at Wk28. Median change from baseline for JADAS 27, 10, 27, & 71 was -14.20, -16.60, & -20.32, respectively at Wk28. JADAS defined minimal disease activity was met by 15% of patients at Wk28. Proportion of JIA ACR 30, 50, 70, & 90 responders at Wk28 was 83.5%, 79.5%, 70.1%, & 46.5%, respectively. 29.1% of patients met criteria for inactive disease at Wk28. Median change from baseline for JADAS 27, 10, 27, & 71 was -14.20, -16.60, & -20.32, respectively at Wk28. JADAS 10, 27, & 71 minimal disease activity was met by 15% of patients at Wk28. Proportion of patients experiencing at least 1 treatment-emergent AE through Wk28 was 77.2%. MedDRA® system organ class with highest incidence of AEs was Infections & infestations (57.5%); most commonly reported AEs were respiratory tract infection (17.3%) then nasopharyngitis (15.0%). Six patients experienced serious AEs through Wk28: Herpes zoster disseminated, Infective exacerbation of bronchiectasis, Sepsis, Variella, Mycosis fungoides, & Suicidal ideation. These events resulted in permanent discontinuation of intravenous golimumab, except for Varicella.

Conclusion: Intravenous golimumab delivered at a dose of 80 mg/m^2 at weeks 0 & 4, then every 8 weeks thereafter and appears to be effective in these patients with a safety profile similar to other TNF inhibitor therapies.

Disclosure of Interests: Niccolò Ruperto Grant/research support from: The Gaslini Hospital, where NR works as full-time public employee, has surveillance of JIA patients exposed to biologics.

FRIO544 Efficacy and Safety of Canakinumab in Systemic Juvenile Idiopathic Arthritis: Experience Using Data of the BIKER Registry

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Background: Canakinumab is approved for the treatment of systemic juvenile idiopathic arthritis (sJIA) older than 2 years.

Objectives: The aim of the German Biologics Registry (BIKER) is the surveillance of JIA patients exposed to biologics.

Methods: Baseline demographics and disease activity parameters were documented. Efficacy was determined using the JADAS and the proposed criteria for inactive disease on medication. Safety assessments were based on reports of adverse events (AE). All reports have been coded according to MedDRA®.

Results: 88 sJIA patients with 82.5 patient-years (PY) of exposure to Canakinumab were recorded in the German BIKER registry. The total observation time (from date of first dose until last follow-up, censored, if another biologic was started) was calculated with 109.9 PY. The cohort treated with Canakinumab had experienced long disease duration of 2.9+/−3.8 years (mean +/- SD). 21 (44%) were pre-treated with methotrexate, 10 (21%) with Etanercept, 3 (6%) with Adalimumab, 19 (38%) with Anakinra and 19 (40%) with Tocilizumab. Comorbidities, 18 (18.8%) received methotrexate, 22 (45.8%) NSAIDs and 23 (48%) systemic corticosteroids.

At last follow up upon treatment, 48%/44%/42%/38% of patients reached PsACR30/50/70/90 improvement. 8 patients (16.7%) had inactive disease according to the Wallace criteria. The median (IQR1-IQR3) of disease activity score was 7.2 (5.0-12.5) at baseline to 3.0 (0.0-3.0) after 24 weeks of treatment. During ongoing treatment, approximately 82% of patients achieved a JADAS defined minimal disease activity; while 64% reached a JADAS defined remission at last follow-up.

125 adverse events (AE) were recorded (114 events/100PY [95% CI 96-144]), of which 38 were serious adverse events (SAEs) [20/100PY [13-30]]. 100 AEs were observed during treatment or up to 90 days follow up after the last exposure to Canakinumab [121/100PY [99-147]]. 19 qualified as SAE (23/100PY [15-36]). Adverse Events of Special Interest were serious and medically important infection (n=4), cytopenia (n=4), macrophage activation syndrome (n=3). There was no opportunistic infection, intestinal perforation, anaphylaxis or other hypersensitivity, thrombotic event, evolving autoimmune disease, cardiac or cerebral event, bleeding, malignancy, or death. A total of 38 patients (79%) discontinued treatment, 8 (17%) due to lack or efficacy, 16 (33%) due to remission and 2 (4%) because of intolerance.

Conclusion: The current analyses adds to the established safety profile of Canakinumab and demonstrates that safety was comparable and consistent with the overall AE profile of Canakinumab in paediatric patients.

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