



XLIX
CONGRESSO
NAZIONALE
AIEOP

HLH e MAS: il punto di vista del reumatologo

Angelo Ravelli

IRCCS Istituto Giannina Gaslini & Università degli Studi di
Genova, Genova

Bologna, 2 ottobre 2024



Il sottoscritto Angelo Ravelli

ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato-Regione del 5 novembre 2009,

dichiara

che negli ultimi due anni ha avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

- *Abbvie, Alexion, Galapagos, Novartis, Pfizer, Reckitt-Benkiser, Sobi*



Agenda of the talk

- Diagnostic/classification criteria for MAS in sJIA
- The MH score
- Recent therapeutic advances



Pediatric diseases in which MAS may occur

- **Systemic juvenile idiopathic arthritis**
- Juvenile systemic lupus erythematosus
- Kawasaki disease
- Juvenile dermatomyositis
- Autoinflammatory syndromes

Diagnostic issues

- MAS is a serious, life-threatening complication
- Early recognition and treatment are critical
- **However, early diagnosis can be difficult**
- **Differential diagnoses:** disease flares, infections, medication side effects

Preliminary diagnostic guidelines for MAS complicating sJIA

Laboratory criteria	Clinical criteria
<ul style="list-style-type: none">▪ Decreased PLT ($\leq 262 \times 10^9$)▪ Elevated GOT/AST (> 59 mU/L)▪ Hypofibrinogenemia (≤ 2.5 g/L)▪ Decreased WBC ($\leq 4.0 \times 10^9$/L)	<ul style="list-style-type: none">▪ Hemorrhages (purpura, easy bruising, mucosal bleeding)▪ CNS dysfunction (irritability, disorientation, lethargy, headache, seizures, coma)▪ Hepatomegaly (≥ 3 cm below the costal arch)
Histopathologic criterion	
Hemophagocytosis in the bone marrow	
Diagnostic rule	
<p>The diagnosis of MAS requires the presence of any 2 of the 4 laboratory criteria. A BM aspirate for the demonstration of macrophage hemophagocytosis may be required only in doubtful cases</p>	

Limitations of preliminary diagnostic guidelines

- Retrospective/literature data for most patients
- Lack of several laboratory measurements in a number of patients
- Insufficient data for some laboratory parameters
- Lack of validation

HLH-2004 diagnostic guidelines

1. Fever
 2. Splenomegaly
 3. Cytopenia (at least 2 of the 3):
 - HB < 90 g/l
 - PLT < 100 x 10⁹ /l
 - Neutrophils < 1,0 x 10⁹ /l
 4. Hypertriglyceridemia and/or hypofibrinogenemia:
 - TG ≥ 265 mg/dl
 - Fibrinogen ≤ 1.5 g/l
 5. Hemophagocytosis in BM, spleen or LN (no evidence of malignancy)
 6. Low or absent NK cell activity
 7. Ferritin ≥ 500 ng/ml
 8. Soluble CD25 ≥ 2,400 U/ml
-

Diagnostic rule: HLH is diagnosed when at least 5 criteria are met

Limitations of HLH-2004 diagnostic guidelines for use in MAS

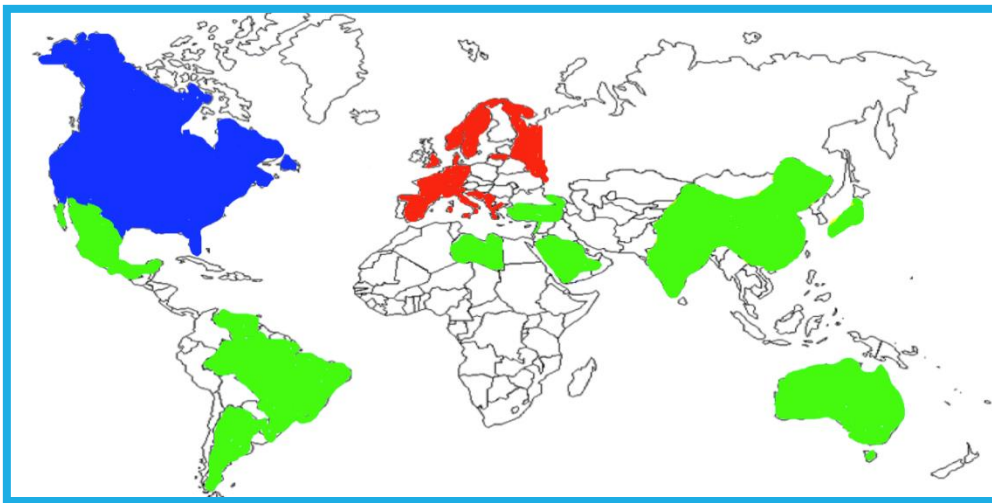
- Thresholds for cytopenia and hypofibrinogenemia too low
- Ferritin level often above ≥ 500 ng/ml in active systemic JIA without MAS
- Hemophagocytosis not always looked for
- NK cell and sCD25 assessments costly and not readily available in all centers

International consensus conference on MAS classification criteria

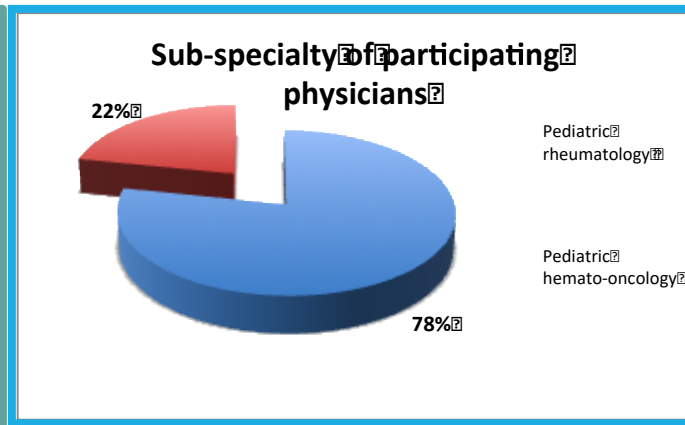
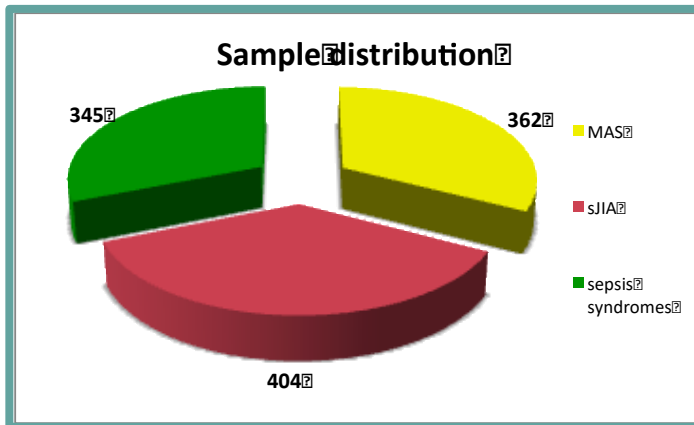
Villa Quartara della Castagna, Genoa, Italy, 21-22 March 2014







- Retrospective cohort of **1111 patients**
- **95** investigators from **33** countries
- Web-based database housed at coordinating center (Gaslini Institute, Genoa)



2016 EULAR/ACR/PRINTO Classification Criteria for MAS Complicating Systemic JIA

A febrile patient with known or suspected systemic JIA
is classified as having MAS if the patient has:

Ferritin > 684 ng/L

AND

at least 2 of the following 4 laboratory abnormalities:

- Platelets $\leq 181 \times 10^9$ /mL
- AST > 48 U/L
- Triglycerides > 156 mg/dL
- Fibrinogen ≤ 360 mg/mL

Development and Initial Validation of the Macrophage Activation Syndrome/Primary Hemophagocytic Lymphohistiocytosis Score, a Diagnostic Tool that Differentiates Primary Hemophagocytic Lymphohistiocytosis from Macrophage Activation Syndrome

Francesca Minoia, MD¹, Francesca Bovis, PhD², Sergio Davì, MD¹, Antonella Insalaco, MD³, Kai Lehmborg, MD⁴, Susan Shenoi, MD⁵, Sheila Weitzman, MD⁶, Graciela Espada, MD⁷, Yi-Jin Gao, MD⁸, Jordi Anton, MD⁹, Toshiyuki Kitoh, MD¹⁰, Ozgur Kasapcopur, MD¹¹, Helga Sanner, MD¹², Rosa Merino, MD¹³, Itziar Astigarraga, MD¹⁴, Maria Alessio, MD¹⁵, Michael Jeng, MD¹⁶, Vyacheslav Chasnyk, MD¹⁷, Kim E. Nichols, MD¹⁸, Zeng Huasong, MD¹⁹, Caifeng Li, MD²⁰, Concetta Micalizzi, MD¹, Nicolino Ruperto, MD, MPH¹, Alberto Martini, MD¹, Randy Q. Cron, MD²¹, Angelo Ravelli, MD^{1,2,*}, and AnnaCarin Horne, MD^{22,*}, on behalf of the Pediatric Rheumatology International Trials Organization, the Childhood Arthritis and Rheumatology Research Alliance, the Pediatric Rheumatology Collaborative Study Group, and the Histiocyte Society[†]

Table I. Comparison of demographic, clinical, laboratory, and histopathologic features at disease onset between patients with MAS and pHLH

	n	Patients with MAS (n = 362)	n	Patients with pHLH (n = 258)	P value
Demographic characteristics					
Median (1st-3rd quartile) age, y	362	8.1 (4.0-13.0)	258	0.3 (0.2-1.2)	<.0001
Female	362	208 (57.5)	258	128 (49.6)	.05
Clinical manifestations					
Fever	355	341 (96.1)	257	236 (91.8)	.03
Hepatomegaly	350	245 (70.0)	254	234 (92.1)	<.0001
Splenomegaly	347	201 (57.9)	248	142 (96.2)	<.0001
Generalized lymphadenopathy	346	178 (51.4)	110	28 (25.5)	<.0001
CNS involvement	349	122 (35.0)	253	90 (35.6)	.88
Jaundice	351	49 (14.0)	99	15 (35.4)	<.0001
Median (1st-3rd quartile) values of laboratory tests					
Hemoglobin, g/dL	335	9.8 (8.3-11.1)	248	7.3 (6.3-8.2)	<.0001
Neutrophil count, $\times 10^9/L$	297	5.4 (2.3-11.5)	221	0.6 (0.3-1.1)	<.0001
Platelet count, $\times 10^9/L$	338	144 (86-270)	249	29 (16-52)	<.0001
Aspartate aminotransferase, U/L	327	134 (58-339)	215	171 (88-376)	.01
Lactate dehydrogenase, U/L	269	1230 (666-2345)	211	696 (487-1249)	<.0001
Triglycerides, mg/dL	278	234 (151-320)	236	325 (221-486)	<.0001
Albumin, g/dL	258	3.1 (2.6-3.5)	189	2.7 (2.3-3.1)	<.0001
Bilirubin, mg/dL	230	0.7 (0.4-1.6)	216	0.5 (0.2-1.7)	.05
Fibrinogen, mg/dL	294	267 (151-440)	224	98 (60-156)	<.0001
Ferritin, ng/mL	308	5353 (1500-13 080)	225	2910 (1400-7270)	.003
Histopathologic features					
Bone marrow aspiration and/or other biopsy	348	252 (72.4)	254	251 (98.8)	<.0001
Hemophagocytosis	252	159 (63.1)	247	191 (77.3)	.0006

CNS, central nervous system.

Except where indicated otherwise, data are n (%).

Table III. Best fitted model of multivariate analysis (n = 338) and attributions of points for the MH score

	OR	95% CI	β	Points in MH score
Age at onset ≤ 1.6 y	40.3	10.8-150.3	3.7	37
Neutrophil count $\leq 1.4, \times 10^9/L$	39.3	10.7-144.8	3.7	37
Fibrinogen ≤ 131 , mg/dL	4.4	1.6-12.5	1.5	15
Splenomegaly	3.3	1.0-10.9	1.2	12
Platelet count $\leq 78, \times 10^9/L$	3.1	1.1-8.6	1.1	11
Hemoglobin ≤ 8.3 , g/dL	2.9	1.1-7.9	1.1	11

The area under the curve of the model is 0.98.

Table V. Probability of pHLH according to the MH score

MH scores	Probability of pHLH (%)
0	<1
11	1.3
12	1.4
15	1.9
22	3.5
23	3.8
26	5.0
27	5.4
34	9.6
37	12.4
38	13.5
48	28.1
49	29.9
52	36.0
59	51.6
60	53.9
64	62.8
71	76.2
74	80.8
75	82.2
85	92.0
86	92.7
97	97.2
100	97.9
108	99.0
111	99.2
112	99.3
123	99.7

The best cutoff value for the MH score was ≥ 60 , with a sensitivity of 91% and a specificity of 93% in discriminating pHLH from MAS.

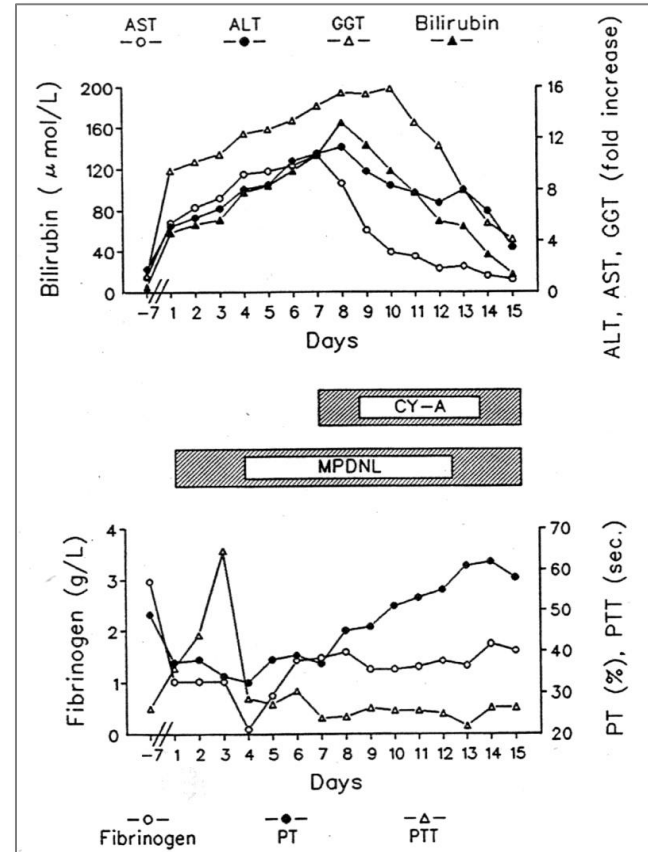
Management

- **Mainstay**

- High-dose iv methylprednisolone (2-6 mg/kg/day in 2-6 divided doses or 10-30 mg/kg iv pulses)

Management

- Cyclosporin A
(oral or iv)

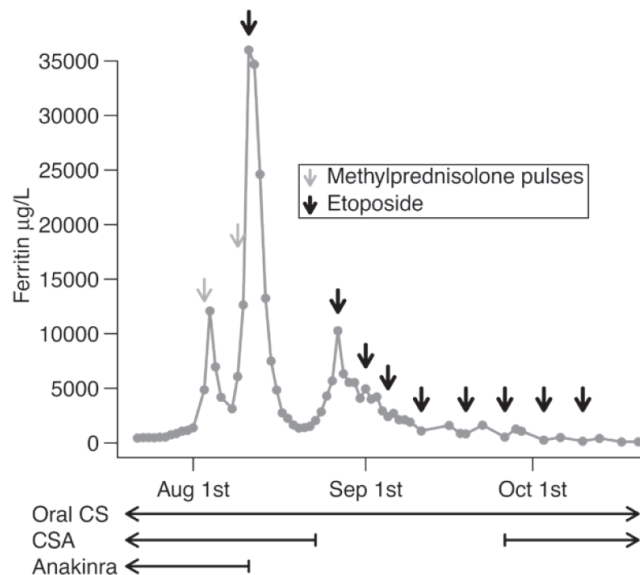


Efficacy of Moderately Dosed Etoposide in Macrophage Activation Syndrome–Hemophagocytic Lymphohistiocytosis

AnnaCarin Horne¹, Tatiana von Bahr Greenwood², Samuel C.C. Chiang³, Marie Meeths¹, Caroline Björklund⁴, Maria Ekelund⁵, Peter Erensjö⁶, Stefan Berg⁷, Stefan Hagelberg⁸, Yenan T. Bryceson³, Ulf Andersson⁸, and Jan-Inge Henter²

7 pts with rapidly progressing MAS and CNS or pulmonary involvement. Three had sJIA, 2 atypical sJIA, and 2 SLE

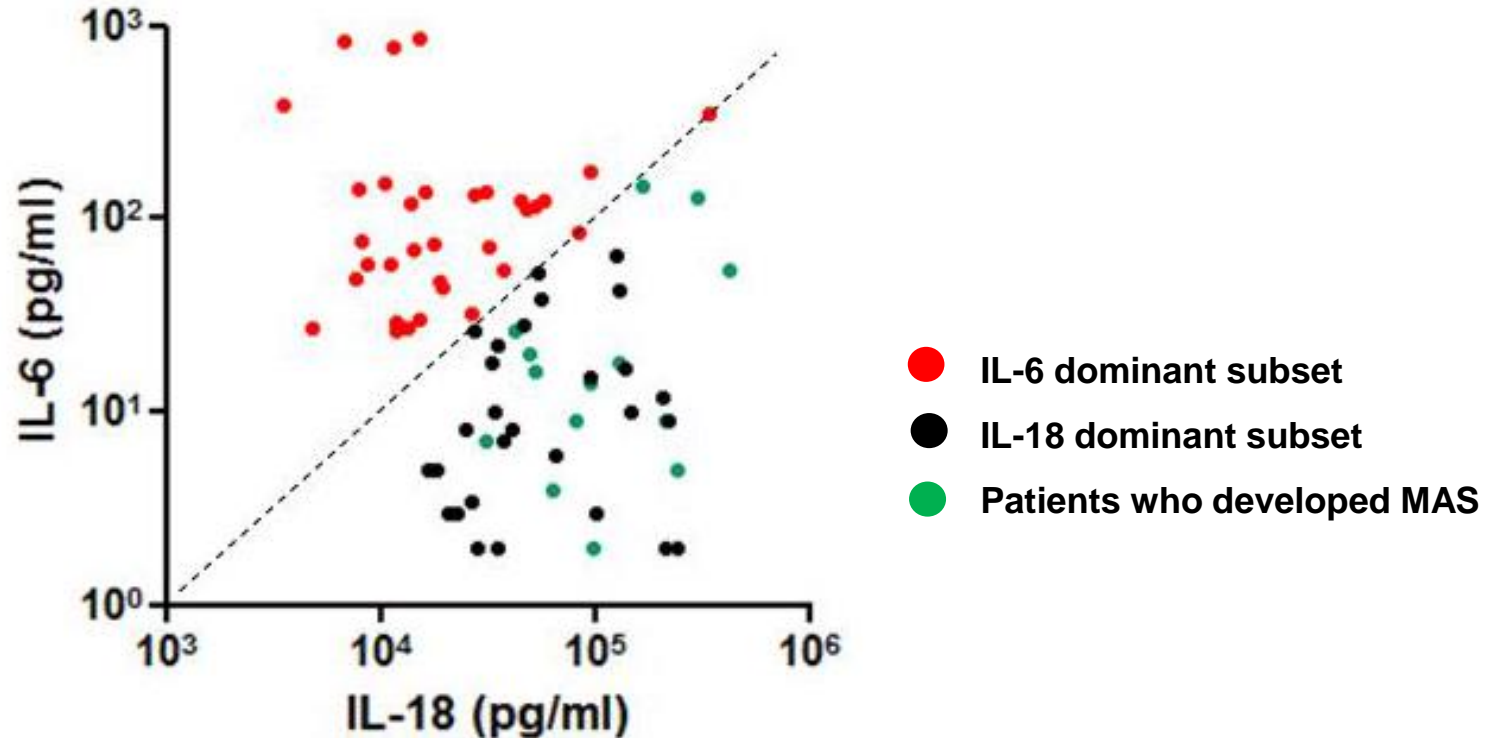
Mean cumulative etoposide dose 671 mg/m² vs 1500 mg/m² recommended in the first 8 weeks of HLH-94/2004 protocols



All pts alive at FU after 2-9 yrs, neurological symptoms normalized in 5 pts

Moderate-dose etoposide recommended in: 1) severe rapidly progressive, fulminant, or refractory MAS-HLH despite anakinra treatment, and (2) MAS-HLH with CNS involvement when an immediate effect is essential, and then possibly in combination with anakinra.



Distinct subsets of systemic JIA based on their cytokine profile



Continuous Intravenous Anakinra Infusion to Calm the Cytokine Storm in Macrophage Activation Syndrome

Luke Adam Monteagudo,¹ Aaron Boothby,² and Elie Gertner¹ 

Benefit of Anakinra in Treating Pediatric Secondary Hemophagocytic Lymphohistiocytosis

Esraa M. Elseily,¹ Peter Weiser,² Courtney B. Crayne,²  Hilary Haines,² Melissa L. Mannion,² Matthew L. Stoll,² Timothy Beukelman,² T. Prescott Atkinson,² and Randy Q. Cron² 

Viewpoint



Silencing the cytokine storm: the use of intravenous anakinra in haemophagocytic lymphohistiocytosis or macrophage activation syndrome

Puja Mehta, Randy Q Cron, James Hartwell, Jessica J Manson*, Rachel S Tattersall*

Lancet Rheumatol 2020;
2: 358-62

The term cytokine storm syndromes describes conditions characterised by a life-threatening, fulminant hypercytokinaemia with high mortality. Cytokine storm syndromes can be genetic or a secondary complication of autoimmune or

COMMENTARY


Intravenous Anakinra for Macrophage Activation Syndrome May Hold Lessons for Treatment of Cytokine Storm in the Setting of Coronavirus Disease 2019

Theresa L. Wampler Muskardin 

SHORT REPORT

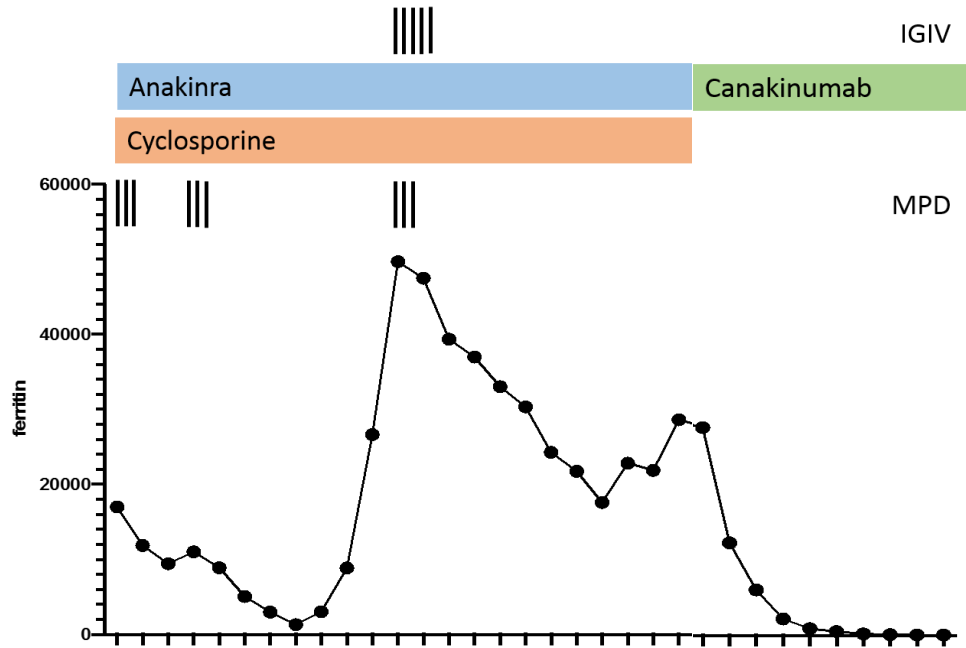
Open Access

Intravenous administration of anakinra in children with macrophage activation syndrome

Omkar Phadke^{1,2*} , Kelly Rouster-Stevens^{1,2}, Helen Giannopoulos², Shanmuganathan Chandrakasan^{1,2} and Sampath Prahalad^{1,2}



Canakinumab & MAS





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CLINICAL SCIENCE

Efficacy and safety of emapalumab in macrophage activation syndrome






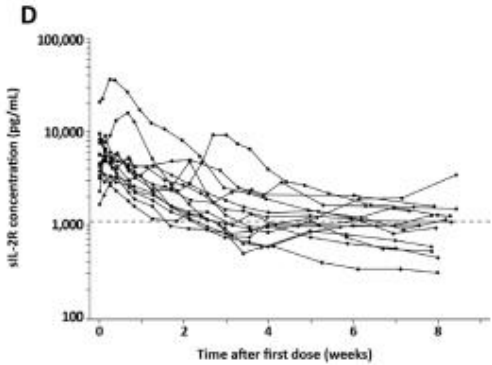
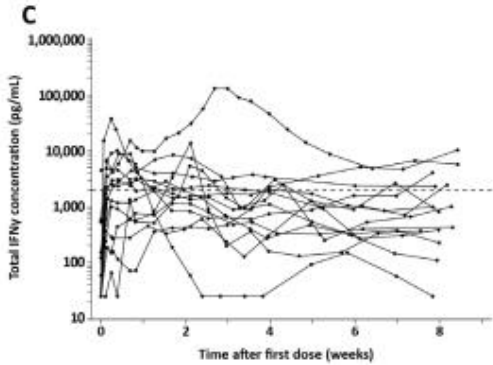
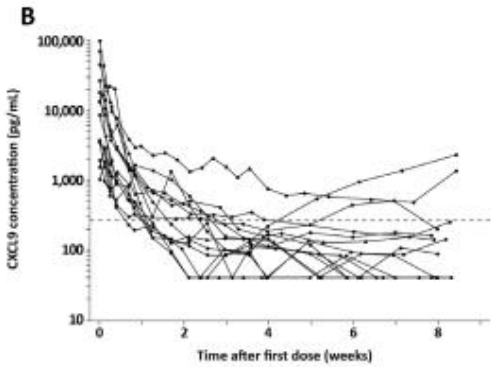
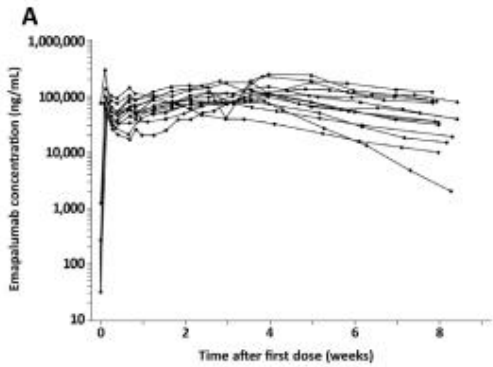
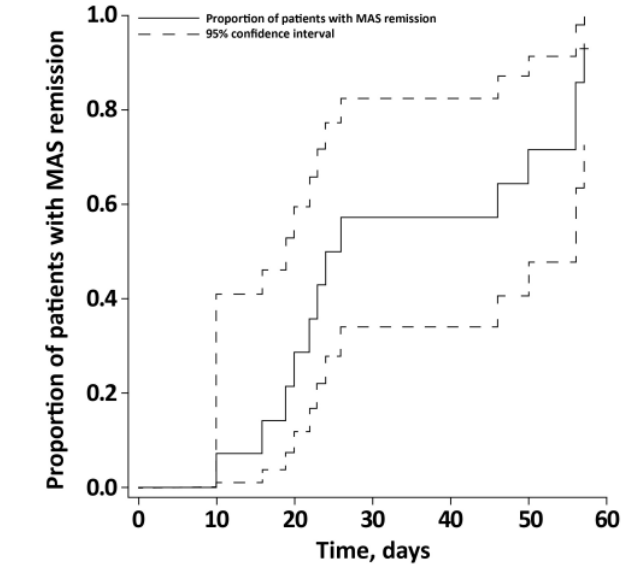
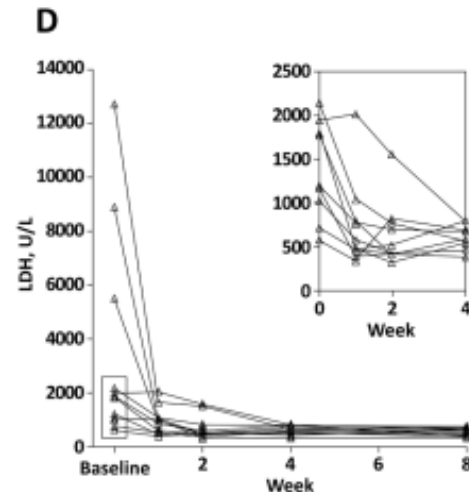
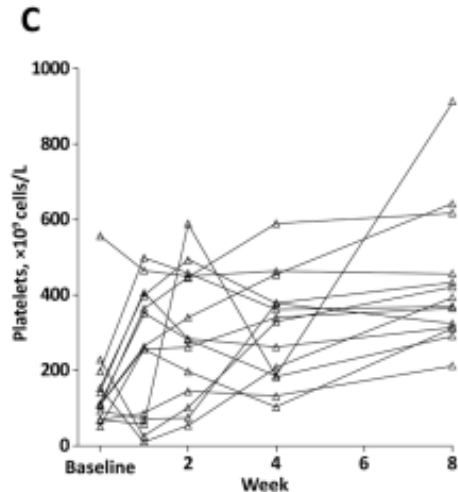
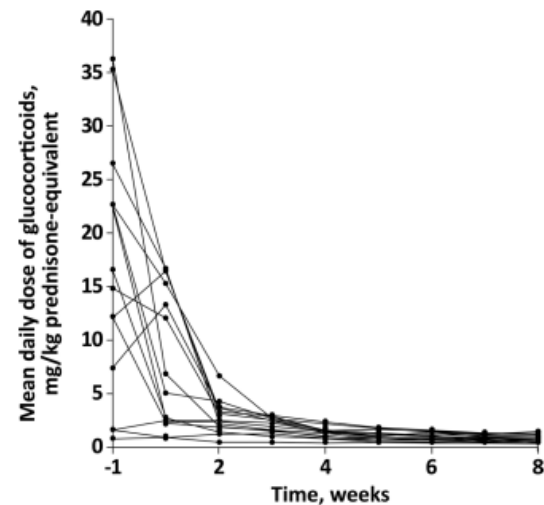
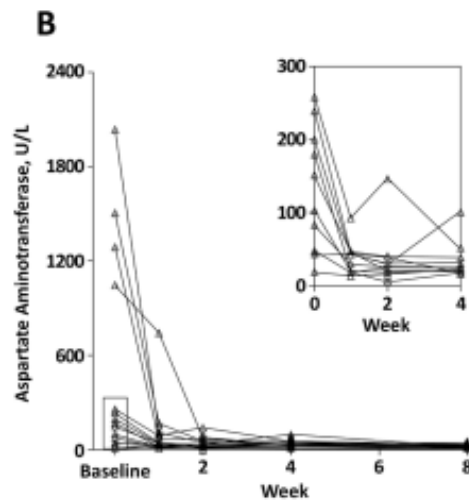
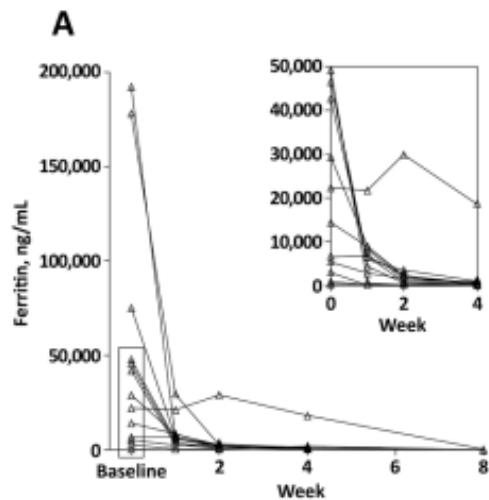
Fabrizio De Benedetti ¹, Alexei A Grom ^{2,3}, Paul A Brogan ⁴,
Claudia Bracaglia ¹, Manuela Pardeo,¹ Giulia Marucci,¹ Despina Eleftheriou,⁴
Charalampia Papadopoulou ⁴, Grant S Schulert ^{2,3}, Pierre Quartier,^{5,6}
Jordi Antón ^{7,8}, Christian Laveille,⁹ Rikke Frederiksen,¹⁰ Veronica Asnaghi,¹⁰
Maria Ballabio,¹⁰ Philippe Jacqmin,¹¹ Cristina de Min¹⁰

Table 1 Baseline demographics and clinical characteristics of the patients

Demographic	(n=14)
Age, years, median (range)	11.0 (2–25)
Sex, female, n (%)	10 (71.4)
Weight, kg, median (range)	45.9 (12.0–68.8)
Age at diagnosis of sJIA/AOSD, years, median (range)	10.5 (1–17)
Previous MAS episodes	
Patients with previous MAS episodes, n (%)	6 (43%)
Total number of previous MAS episodes	19
Number of MAS episodes per patient*	3 (1–6)
Treatment of the current MAS episode prior to emapalumab	
High-dose intravenous glucocorticoids, n (%)	14 (100)
Average daily dose during week –1, † mg/kg prednisone-equivalent, median (range)	15.7 (0.8–36.4)
Ciclosporin, ‡ n (%)	8 (57.1%)
Anakinra, ‡ n, (%)	7§ (50)
Average daily dose during week –1, † mg/kg, median (range)	4.2 (1.6–13.9)
IVIG, n (%)	3 (21.4)





Safety

- 6 viral events in 3 patients (two infections and four positive tests) related to emapalumab.
- One cytomegalovirus (CMV) reactivation reported as serious.
- In total, there were 5 CMV events (three reactivations, 1 infection and 1 positive test with no symptoms).
- All viral events resolved spontaneously or with standard treatment.

IMMUNOBIOLOGY AND IMMUNOTHERAPY

Interleukin-18 diagnostically distinguishes and pathogenically promotes human and murine macrophage activation syndrome

Eric S. Weiss,^{1,*} Charlotte Girard-Guyonvarc'h,^{2,*} Dirk Holzinger,^{3,4} Adriana A. de Jesus,⁵ Zeshan Tariq,⁶ Jennifer Picarsic,⁷ Eduardo J. Schiffrin,⁸ Dirk Foell,³ Alexei A. Grom,⁹ Sandra Ammann,¹⁰ Stephan Ehl,¹⁰ Tomoaki Hoshino,¹¹ Raphaela Goldbach-Mansky,⁵ Cem Gabay,² and Scott W. Canna¹

¹RK Mellon Institute, Children's Hospital of Pittsburgh of UPMC/University of Pittsburgh, Pittsburgh, PA; ²Division of Rheumatology, Department of Internal Medicine Specialties, University Hospital of Geneva, Geneva, Switzerland; ³Department of Pediatric Rheumatology and Immunology, University Children's Hospital Muenster, Muenster, Germany; ⁴Department of Pediatric Hematology-Oncology, University of Duisburg-Essen, Essen, Germany; ⁵Translational Autoinflammatory Diseases Studies, National Institute of Allergy and Infectious Diseases, and ⁶Molecular Immunology and Inflammation Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD; ⁷Department of Pathology, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA; ⁸AB2Bio, Ltd., Lausanne, Switzerland; ⁹Pediatric Rheumatology, Cincinnati Children's Hospital, Cincinnati, OH; ¹⁰Center for Chronic Immunodeficiency, Faculty of Medicine, University of Freiburg, Freiburg, Germany; and ¹¹Division of Respiratory, Neurology, and Rheumatology, Kurume University School of Medicine, Kurume, Japan

Correspondence

IL-18 binding protein reverses the life-threatening hyperinflammation of a baby with the NLRC4 mutation



To the Editor:

We read with excitement the article titled “Life-threatening NLRC4-associated hyperinflammation successfully treated with Interleukin-18 inhibition” by Canna et al.¹ We congratulate the authors for this outstanding diagnostic and therapeutic triumph. This article also represents translation from the bench of a unique protein, the IL-18 binding protein (IL-18BP),² into a

investigators do not measure IL-18BP and therefore the level of free IL-18 remains unclear regarding any relation to disease severity.

Daniela Novick, PhD^a

Charles A. Dinarello, MD^b





From ^athe Weizmann Institute of Science, Molecular Genetics, Rehovot, Israel; and ^bthe Department of Medicine, University of Colorado Denver, Aurora, Colo. E-mail: daniela.novick@weizmann.ac.il.

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Basic science

Long-term efficacy of MAS825, a bispecific anti-IL1 β and IL-18 monoclonal antibody, in two patients with systemic JIA and recurrent episodes of macrophage activation syndrome

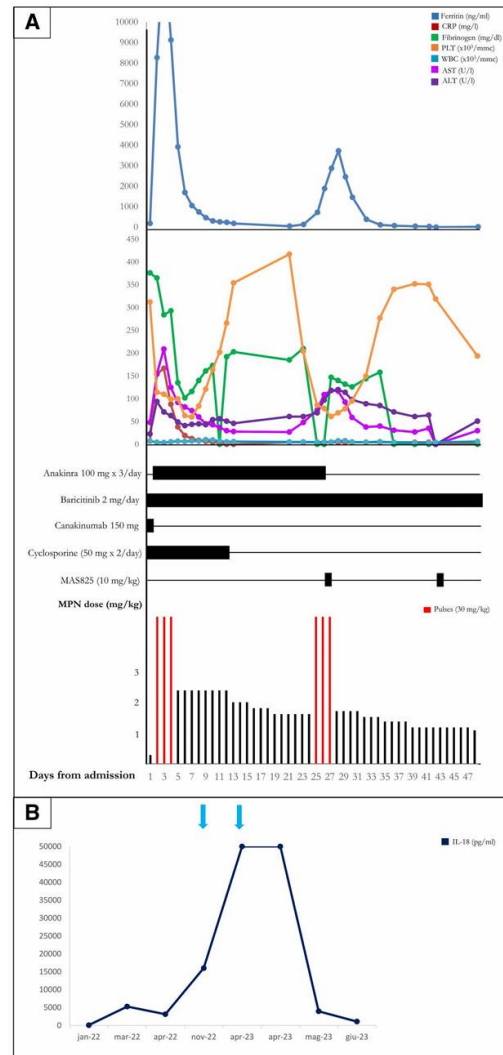
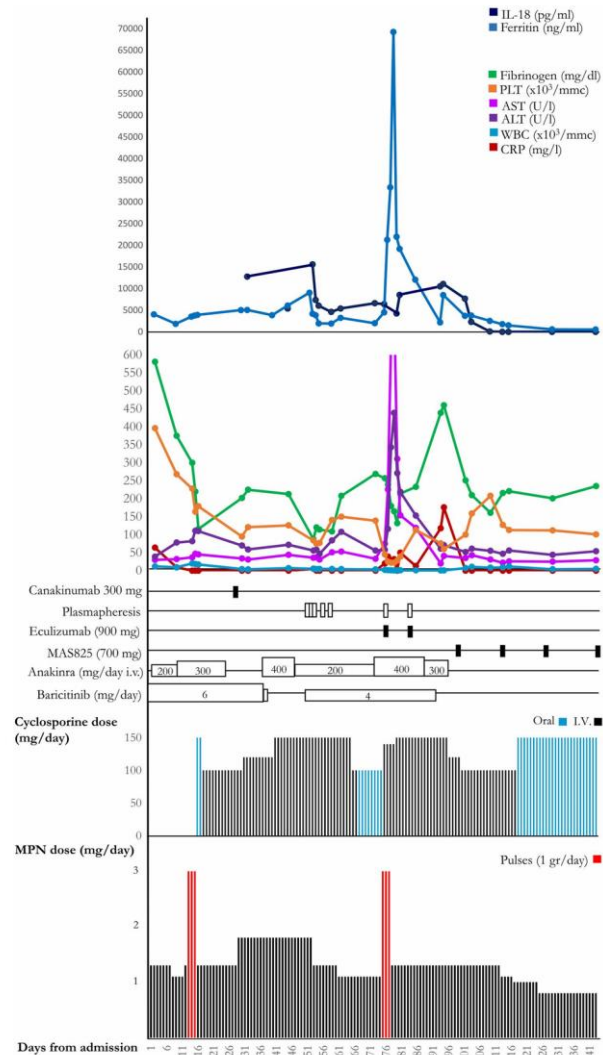
Roberta Caorsi ^{1,2,*}, **Arinna Bertoni**¹, **Caterina Matucci-Cerinic** ^{1,2}, **Valentina Natoli**^{1,2},
Serena Palmeri², **Silvia Rosina**¹, **Federica Penco**¹, **Clara Malattia**^{1,2}, **Alessandro Consolaro**^{1,2},
Stefania Viola¹, **Riccardo Papa** ¹, **Anna Corcione**¹, **Stefano Volpi**^{1,2}, **Angelo Ravelli**^{2,3},
Marco Gattorno ¹

¹Rheumatology and Autoinflammatory Diseases, IRCCS Istituto Giannina Gaslini, Genova, Italy

²Dipartimento di Neuroscienze, Riabilitazione, Oftalmologia, Genetica e Scienze Materno-Infantili (DiNOGMI), Università degli Studi di Genova, Genova, Italy


³Scientific Direction, IRCCS Istituto Giannina Gaslini, Genova, Italy

*Correspondence to: Roberta Caorsi, Reumatologia e Malattie Autoinfiammatorie, IRCCS Istituto Giannina Gaslini, via Gaslini 5, 16148 Genova, Italy.
E-mail: robertacaorsi@gaslini.org



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Grazie

angeloravelli@gaslini.org