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26th PRINTO newsletter | September 2017

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PRINTO news

Annual PRINTO General meeting at PReS 2017

Dear Friends,

we are glad to invite all of you to the upcoming Annual PRINTO General meeting at PReS 2017!

The PRINTO meeting will be held from 2.00 to 3.00 pm on Friday, 15th September 2017, in Room MC3 of the Megaron Athens International Conference Centre - MAICC, Vass. Sofias & Kokkali in Athens, Greece.

Here is the agenda:

- **Introduction (A. Martini)**
- **Update on PRINTO Projects (N. Ruperto)**
- **Pharmachild (N. Wulffraat, J. Swart, N. Ruperto)**
- **SHARE (P. Dolezalova, N. Wulffraat)**
- **EPOCA (A. Ravelli, A. Consolaro)**
- **OMERACT JIA Core Set Working Group (A. Consolaro)**
- **The EuroFever Registry (M. Gattorno, S. Federici)**
- **Update on the European Research Network (ERN/RITA) (T. Avcin, M. Gattorno)**
- **MYPAN (D. Eleftheriou)**

See you soon at the 24th Paediatric Rheumatology European Society Congress (PReS 2017) in Athens!

PRINTO ongoing projects

PharmaChild

Juvenile idiopathic arthritis (JIA) is the most common chronic paediatric rheumatic disease and an important cause of short and long-term disability and quality of life impairment. Methotrexate (MTX) is the second line agent of first choice for the treatment of children with polyarticular JIA who do not respond to NSAIDs.

Patients with JIA who do not respond or are intolerant to MTX are candidates for the treatment with biologic agents such as etanercept, infliximab, adalimumab, abatacept and others currently in development. However, little information exists on the long term safety of these agents that are currently being used in children with JIA.

Pharmachild is a pharmacovigilance project which aims at observing children with JIA for 3-10 years undergoing treatment with MTX or biologic agents in order to collect moderate, severe or serious adverse events occurred.

This project is conducted by the participating centres of the more than 50 countries belonging to the Paediatric Rheumatology INternational Trials Organisation (PRINTO, certified ISO 9001-2008), or the Pediatric Rheumatology European Society (PRES). More than 200 PRINTO centres worldwide have already expressed their interest in participating to the project.

Pharmachild has been funded by the European Union (EU) within the FP7 framework (contract number 260353, principal investigator Dr Nico Wulffraat, co-principal investigator Dr Nicolino Ruperto).

The Pharmachild study has obtained the ENCePP Study Seal (ENCePP). The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP®) is a collaborative scientific network coordinated by the European Medicines Agency and developed in collaboration with European experts in the fields of pharmacoepidemiology and pharmacovigilance. The ENCePP Study Seal means that a study upholds high standards throughout the research process based on the principles of transparency and scientific independence.

At present...
Currently the PharmaChild registry includes the prospective data of more than 3200 patients and the retrospective data of more than 8000 patients coming from more than 60 centres located in over 30 countries worldwide

COLLABORATION WITH PHARMACEUTICAL COMPANIES
The Pharmachild protocol envisages the opportunity of a cooperation with pharmaceutical companies, which may want to use the data derived from Pharmachild for regulatory post-marketing surveillance obligations related to their product towards regulatory authorities. In this cases, PRINTO will MAINTAIN THE OWNERSHIP OVER THE DATA COLLECTED in order to continue to fulfill the ENCePP principles of transparency and scientific independence. All related possible revenues will be totally reinvested for the research needs of the project to support the prolongation of the registry over the planned 3-10 years. List of companies which have agreed to cooperate with Pharmachild: - Bristol-Myers Squibb (Abatacept in JIA).

At present...
As of today the Abatacept JIA Registry sponsored by Bristol-Myers Squibb has enrolled more than 170 patients in the over 20 centres belonging to the PRCSG group in Canada and US and more than 220 patients in the over 30 centres belonging to the PRINTO network in Europe and rest of the world.

EPOCA

By involving more than 50 countries belonging to the network of Paediatric Rheumatology INternational Trials Organisation (PRINTO certified ISO 9001-2008, www.printo.it) EPOCA (EPidemiology, treatment and Outcome of Childhood Arthritis) aims to devise a new tool that enables the multidimensional assessment of the disease status in children with JIA. This new instrument, named Juvenile Arthritis Multidimensional Assessment Report (JAMAR), is simple easy to apply and multidimensional in nature. JAMAR?s objectives are to foster the use of standardized quantitative outcome measures in daily care and to enable comparability of outcome data across different centers. Most clinical measures currently used to assess the disease status, particularly functional ability and health-related quality of life questionnaires, are lengthy and complex. According to agreed international guidelines JAMAR will be widely agreed upon and translated, cross-culturally adapted and validated in different languages by the PRINTO coordinators.

Primary objectives
Outcome
- To translate, cross-culturally adapt and validate the JAMAR in the language of each participating countries
- To compare the current outcomes of children with JIA across continents and countries.

Secondary objectives
Epidemiology
-To characterize and compare the frequency of the JIA categories in different countries and in different continents.
-To describe and compare the prevalence of iridocyclitis in different continents and in different countries.
-To define and compare the prevalence of ANA in the different JIA categories across diverse areas of the world.

Treatment
-To compare the treatments used in the management of children with JIA in different countries.

-To obtain information on the access to biologic medications in different countries.
-To compare the same outcomes by disease category.

Outcome
-To promote regular use of quantitative measures, either physician-centred or parent/patient-centred, in the assessment of children with JIA in standard clinical practice.
-To foster uniformity and standardization of clinical assessment of children with JIA across different countries.

At present...
PRINTO is glad to announce that **the last batch of 11 JAMAR papers will be finalized and submitted to Rheumatology International by the end of october, while the first batch of 39 papers was sent to the Journal last april.** These **50 papers** will be part of a dedicated supplement of the Journal on patient's reported outcomes (PRO)s.
The supplement will contain one paper for each cross-culturally adapted and validated version of the JAMAR (for instance "The Italian version of the JAMAR") and a general introductive manuscript with the description of the methodological approach. This methodological paper is currently in draft and will include the data related to the 39 countries for which the analysis has been already completed and will be progressively updated with the data of the the remaining 11 manuscripts still in progress.
The authorship of each manuscript is defined according to PRINTO policy and ICMJE recommendations for authorship and completed with local input. The main responsible of the project in each country is listed in the first positions followed by the remaining significant authors. Additional people are listed in the acknowledgment section.

Globally, for EPOCA, **PRINTO has collected** by now **more than 9000 JIA patients and almost 5000 healthy controls from 125 centres in 50 countries** .
Thanks to all the participating centres for their effort and contribution within the EPOCA study!

If you are interested in the project, please contact the PRINTO coordinating centre for the complete set of information (material for ethics committee submission, protocol, data collection forms).

ABIRISK

ABIRISK (Anti-Biopharmaceutical Immunization: Prediction and Analysis of Clinical Relevance to Minimize the Risk), is a large European project funded by the Innovative Medicines Initiative (IMI), the study completed the enrollment in March 2016 and has the aim to provide an integrated approach to investigate anti-drug antibody (ADA) formation in Juvenile Idiopathic Arthritis (JIA), adult rheumatoid arthritis and other conditions treated with biopharmaceuticals (BPs). Several BPs are available today for the treatment of many severe diseases including JIA. A major limitation to the use of BPs is the development of anti-drug antibodies in a subset of patients. The prediction, prevention and cure of anti-drug immunogenicity are major goals in BP drug development and patient safety.

The ABIRISK Consortium, composed of 36 partners from both academia and industry, brought together a large network of adult and paediatric clinicians from various specialties with broad experience in the care of patients treated with BP known to develop ADA, access to clinical samples from large cohorts of treated patients, renowned academic scientists, immunologists, biologists, database experts, statisticians and leading companies of European Federation of Pharmaceutical Industries and Associations (EFPIA).

PRINTO managed this project as a sub-study of PharmaChild for the JIA Cohort enrollment in the study and succeeded to collect the biologic samples (Serum and RNA) of 147 children with juvenile idiopathic arthritis newly treated with adalimumab (80 patients), etanercept (35 patients) or tocilizumab (32 patients) at start of therapy and at 4 follow-up visits during the first year of treatment, with an extra visit between month 15 and month 18.

The samples shipment from local laboratories is now in progress: the frozen samples are sent to the PRINTO facilities in Genoa (Italy) and they will be transferred to the ABIRISK consortium for antibodies evaluation. The clinical data are the data collected for the PharmaChild registry.

For further information, you can contact the PRINTO office.

Download ABIRISK brochure.

SHARE

The "Single Hub and Access point for paediatric Rheumatology in Europe" (acronym SHARE, project number 2011 1202; PI N. Wulffraat) aims to provide the European countries with recommendations for the care of children with rheumatic diseases. These recommendations are based on systematic literature reviews and on the surveys sent by PRINTO to individual centres belonging to its network all over the world.

To identify the specific needs for the optimal care in PRD, PRINTO implemented an online survey, available at www.printo.it/SHARE. In September 2017, 237 paediatric rheumatic centres had already completed the questionnaire.

Thanks to this project, PRINTO has updated and renovated its website for families, launched in 2003 (Ruperto N, et Al. for PRINTO/PRES Printo/Pres international website for families of children with rheumatic diseases: www.pediatric-rheumatology.printo.it. Ann Rheum Dis 2005; 64:1101-1106).

The new site www.printo.it/pediatric-rheumatology launched in December 2015, offers scientific information regarding the pediatric rheumatic diseases (PRD), the list of centres dealing with PRD, and the list of the family associations in more than 60 languages.
The website has been designed to adapt to the various portable devices, and allows all technical supports to browse easily among the contents – from a technical point of view, multimodality and user friendliness have been identified as the main characteristics to satisfy. Being a tool for families and patients, it includes customised illustrations created by professional illustrators, the possibility to share contents via the main social networks and a Search button (also available for voice search on smartphones), along with a map locating the centres and associations via Google Maps.
In order to ease the contents' consultation for the patients and their families, PRINTO has implemented an **APP for Android operating system** . Its design and structure reflect the website, with three main sections.

Parent survey: in order to mirror the survey for physicians and have a clear picture of the standards of care from a patient/parent point of view, a dedicated survey has been prepared in a collaborative effort between Dr Nico Wulffraat and the ENCA (European Network for Children with Arthritis) members. The patient/parent survey has been translated in 18 languages. Currently, almost 1300 patients have completed the SHARE parent survey.

Eurofever Registry

The Eurofever Registry was promoted in 2008 by the work group of autoinflammatory diseases of the Paediatric Rheumatology European Society (PRES) and was supported by the Executive Agency for Health and Consumers (EAHC).

The general aims of the Eurofever project are to:
· sensitive pediatricians and pediatric rheumatologists to the prompt recognition of Autoinflammatory Diseases;
· provide proper information to families affected by these conditions;
· increase the knowledge on the clinical presentation, response to treatment and complications of theses rare disorders.

The main objective of the project has been the creation of a registry of autoinflammatory diseases.

Two years ago a new section dedicated to Efficacy and Safety has been implemented and the registry is now able to collect also longitudinal information.
New auto - inflammatory diseases have been added, as of today the following conditions are considered by the Project:

· Behçet disease
· Blau's syndrome/Early onset sarcoidosis
· Cryopyrin associated periodic syndrome
· Chronic recurrent multifocal osteomyelitis
· Deficiency of IL-1 receptor antagonist
· Familial Mediterrean Fever
· Mevalonate kinase deficency (Hyper IgD syndrome)
· NLRP12 -associated periodic syndrome
· Pyogenic Sterile Arthritis, Pyoderma Gangrenosum and Acne (PAPA) syndrome
· Tumor necrosis factor receptor-associated periodic syndrome (TRAPS)
· Periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA)
· CANDLE syndrome
· DITRA syndrome
· Schnitzler syndrome
· Majeed syndrome
· Deficiency of Adenosine Deaminase 2 (DADA2)
· STING-asociated vasculopathy with onset in infancy (SAVI)
· CARD14 mediated psoriasis (CAMPS)
· Undefined Periodic fever

Currently Eurofever includes the data of more than 3900 patients coming from 110 centres located in 39 countries worldwide

MYPAN

The MYPAN trial is an Open Label Randomised Controlled Trial of Mycophenolate Mofetil (MMF) Versus Cyclophosphamide (CYC) for the Induction of Remission of childhood PAN sponsored by University College London and coordinated by the Children Hospital in Liverpool and PRINTO (PI Dr P. Brogan). MYPAN will investigate the comparative efficacy and safety of MMF (experimental treatment) vs CYC (standard treatment) for induction of remission of childhood PAN. This will be the first ever randomized trial for childhood PAN. As of today 30 centres (UK and non-UK sites) have shown interest in participating in MYPAN: PRINTO is currently completing the submission procedures to the regulatory

authorities/ethics committees and the sites activation of the non-UK centres. Globally, as of today 11 centres have been activated and have enrolled 7 patients. We are planning to activate other 10 centres in the next few weeks.
Since the enrollment will be officially closed on 31 January 2018, we ask all the participating centres to make a last effort and try to recruite the last patients in the study.

PRINTO patients enrollment

Country	EPOCA	PHARMACHILD	EUROFEVER	ABIRISK Registry
Algeria	120	0	0	0
Argentina	473	123	57	0
Armenia	0	0	101	0
Australia	0	0	13	0
Austria	0	28	27	0
Belgium	199	0	13	0
Brazil	303	393	17	0
Bulgaria	300	57	0	0
Canada	359	0	8	0
Chile	119	0	5	0
China	0	0	14	0
Colombia	10	0	0	0
Croatia	200	174	11	0
Czech Republic	203	119	215	26
Denmark	402	542	135	0
Ecuador	46	25	0	0
Egypt	200	0	0	0
Estonia	210	0	0	0
Finland	273	0	0	0
France	222	305	287	20
Georgia	200	0	9	0
Germany	424	1	299	0
Greece	375	485	148	47
Hungary	297	127	24	0
India	375	119	3	0
Iran, Islamic Republic of	320	0	0	0
Israel	216	89	168	0
Italy	1400	1463	1214	28
Japan	0	0	6	0
Latvia	304	259	6	2
Lebanon	0	0	1	0
Libya	200	0	0	0
Lithuania	217	320	7	0
Mexico	199	65	0	0
Netherlands	317	679	120	0

Norway	375	362	0	4
Oman	143	16	6	0
Paraguay	151	0	0	0
Poland	248	29	9	3
Portugal	109	0	0	0
Romania	411	426	46	1
Russian Federation	298	468	63	0
Saudi Arabia	200	70	39	0
Serbia	349	276	5	0
Slovakia	208	126	1	1
Slovenia	223	53	18	0
South Africa	191	0	0	0
Spain	605	717	250	3
Sweden	144	0	1	0
Switzerland	167	490	95	1
Thailand	206	0	0	0
Turkey	563	1	222	11
Ukraine	200	0	0	0
United Kingdom	200	0	296	0
United States	413	0	6	0
Total	**13887**	**8407**	**3965**	**147**

PRINTO overall enrollment status

PRINTO latest papers

Brunner HI, Ruperto N, Tzaribachev N, Horneff G, Chasnyk VG, Panaviene V, Abud-Mendoza C, Reiff A, Alexeeva E, Rubio-Pérez N, Keltsev V, Kingsbury DJ, Del Rocio Maldonado Velázquez M, Nikishina I, Silverman ED, Joos R, Smolewska E, Bandeira M, Minden K, van Royen-Kerkhof A, Emminger W, Foeldvari I, Lauwerys BR, Sztajnbok F, Gilmer KE, Xu Z, Leu JH, Kim L, Lamberth SL, Loza MJ, Lovell DJ, Martini A.

Subcutaneous golimumab for children with active polyarticular-course juvenile idiopathic arthritis: results of a multicentre, double-blind, randomised-withdrawal trial.

Ann Rheum Dis [Epub ahead of print] PubMed

Ruperto N, Brunner HI, Lovell DJ, Martini A for the Pediatric Rheumatology International Trials Organization (PRINTO) and the Pediatric Rheumatology Collaborative Study Group (PRCSG)

Extrapolation or controlled trials in paediatrics: the current dilemma.

Archives Dis Child [Epub Ahead of print] PubMed

Other news & events

24th Paediatric Rheumatology European Society Congress (PReS 2017)

The 24th Paediatric Rheumatology European Society Congress is approaching! 2017 PReS meeting will be held from 14th to 17th September in Athens.

Continuing the successful trend of past Congresses, the PReS 2017 Congress will feature presentations of some of the most recent research and trials, and will be characterized by robust debates on the clinical challenges of modern pediatric rheumatology.

Moreover, the Congress will provide unique opportunities to network with leadership in Pediatric Rheumatology and enjoy enlightened and innovative learning experiences that highlight the most up-to-date, evidence-based developments in the field.

For more details, please visit the official website of the event:
http://www.pres.eu/pres2017/

PReS EMERGE Fellowship program

Following the 2016 PReS YIM in Genoa, a new group of young paediatric rheumatologists and researchers was founded called PReS EMERGE (EMErging RheumatoloGists and rEsearchers). The overarching aim of the group is to improve clinical and research opportunities for trainees from all over the world working in the field of paediatric rheumatology. The group is currently working on a number of initiatives, with the first to be implemented being the PReS EMERGE Fellowship program.

What is the PReS EMERGE Fellowship program?
This program provides financial and practical assistance for paediatric rheumatology trainees who are members of PReS and younger than 45 years, to facilitate placements of up to 6-months within a European Paediatric Rheumatology Centre. In addition to gaining clinical knowledge and skills, the trainee will be given the opportunity to participate in a research project.
The overall aims of this initiative are to:

- Enhance both clinical and basic collaborative research conducted by trainees within Europe
- Foster a network of emerging and established paediatric rheumatologists
- Allow sharing of ideas and practices between different countries to harmonize paediatric rheumatology training and stimulate collaboration in the field

PROGRAM DEADLINES (for 2017 - 2018):

- Program was announced in May/August 2017
- Application deadline will be 15th of November 2017
- Selected candidates would be announced 6th of December 2017
- The fellowship should begin between February - June 2018

For the program details and other important info please go to:
http://www.pres.eu/activities/young-investigators/fellowship-programs.html

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ERN - RITA

European Reference Networks (ERN) are involving virtual networks healthcare providers across Europe supported by the European Commission. To review a patient's diagnosis and treatment, ERN coordinators will convene a "virtual" advisory board of medical specialists across different disciplines, using a dedicated IT platform and telemedicine tools. This way it is the medical knowledge and expertise that travel, who have the rather than the patients' comfort of staying in their supportive home environments.

RITA (ERN on immunodeficiency, autoinflammatory and autoimmune diseases) is one of the 24 European Reference Networks approved by the ERN Board of Member States.

RITA brings together the leading European centres with expertise in diagnosis and treatment of rare immunological disorders. These constitute potentially life-threatening conditions requiring multidisciplinary care using complex diagnostic evaluation and highly specialised therapies. The network divides these conditions into three sub-themes: primary immunodeficiency (PID), autoimmune disorders and autoinflammatory disorders. In addition, there is a sub-theme of paediatric rheumatology which straddles the autoimmune and autoinflammatory sub-themes.

The foundation of RITA has been developed to bring together the resources and hard work of successful, already existing, highly specialised international scientific societies, registries and websites:

· ESID - European Society for Immune Deficiencies (inc ESID registry)
· PRES - Paediatric Rheumatology European Society (inc Eurofever and Pharmachild registries)
· ISSAID – International Society for Auto-Inflammatory Diseases
· **PRINTO** - Paediatric Rheumatology International Trials Organisation
· EUVAS – European Vasculitis Society
· BEHCET International

The RITA network is currently made up of 24 centres across Europe from 10 different countries:

- Belgium

- Czech Republic
- France
- Germany
- Italy
- Slovenia
- Spain
- Sweden
- The Netherlands
- United Kingdom

Built upon existing networks across Europe, (as PRINTO), we have already begun to develop links with affiliated centres in other countries. For more information about the ERNs and the EU health strategy, please visit http://ec.europa.eu/health/ern

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PRINTO membership

As of today, PRINTO has reached 1330 effective members in 620 centres from 86 countries.
If you wish to become a PRINTO member
and receive regular updates about our research activity and invitations to our projects
please go to:
https://www.printo.it/contact/apply-membership
Your cooperation will be more than welcome
and your effort will be essential for the research in the field of paediatric rheumatic diseases.

WELCOME ABOARD!

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