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28th PRINTO newsletter | September 2018

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PRINTO news

25th European Pediatric Rheumatology Congress (PReS 2018)

The 25th European Pediatric Rheumatology Congress (PReS 2018) will start soon **in Lisbon** , Portugal, **from 5th to 8th September 2018.**
The Congress will take place at the Lisbon Congress Center (CCL) which is located close to the river Tagus and the historical and cultural heritage of Belem, just a few minutes from the city center, in a prime area with a vast transport supply.
In line with previous congresses organized by PReS, this will be a place for challenging presentations and enriching debates of the more recent scientific investigations, including new syndromes and their treatment, trials for old diseases of young people and an up-to-date of care of the more severe juvenile rheumatic diseases.
In this occasion valuable abstracts will be presented both by young and mature Pediatric Rheumatologists from Europe and around the World and they will certainly help to advance the field of Pediatric Rheumatology both in basic science and in clinical practice.
You are warmly invited to attend the PRINTO General Assembly that will take place on Thursday 6 September 2018, from 14.00 to 15.00, in the Auditorium IV.
For more info please go to http://www.pres.eu/pres2018/index.html

PRINTO Annual General Assembly at PReS 2018

Dear Friends,

we are glad to invite all of you to the upcoming Annual PRINTO General meeting at PReS 2018 in Lisbon!
The **PRINTO Annual General Assembly at PReS 2018 will be held on Thursday 6 September 2018, from 14:00 to 15:00, in Auditorium IV.**

Here is the agenda:

- Introduction (A. Martini)
- Update on PRINTO Projects (N. Ruperto)
- JIA classification study (N. Ruperto)
- STARS (A. Consolaro)
- OMERACT JIA Core Set Working Group (A. Consolaro)
- Pharmachild (J. Swart)

- The EuroFever Registry (M. Gattorno)
- Update on the European Research Network (ERN/RITA) (T. Avcin)
- MYPAN (P. Brogan)

See you soon at the 25th Paediatric Rheumatology European Society Congress (PReS 2018) in Lisbon!

2019 Meeting of the International Society of Systemic Autoinflammatory Diseases (ISSAID) in Genoa

Dear Friends,

Many of you will have heard about the tragic incident that Genoa has been living through these past few weeks with the collapse of a section of the Morandi bridge. This is naturally a very hard time, first and foremost for the families of the victims, but also for the people and City of Genoa.

We would like to reassure the ISSAID community that the City of Genoa is nevertheless concentrating efforts into ensuring that the city can continue to function with as little disruption as possible.

I hope to welcome you next year in Genoa **on March 31st- April 3rd, 2019** !
You can click here to see the flyer and go to www.issaid2019.org for more details.

Marco Gattorno
On behalf of the ISSAID Steering Committee

PRINTO ongoing projects

JIA classification study

Juvenile idiopathic arthritis (JIA) is an exclusion diagnosis that encompasses all the forms of otherwise unexplained chronic arthritis occurring under the age of 16. Various attempts have been made to classify this heterogeneous group of diseases with the aim of identifying mutually exclusive categories suitable for etiopathogenetic studies. The classification that is currently used worldwide was proposed in 1995 by the International League of Associations for Rheumatology (ILAR) and contains seven different categories: systemic arthritis, oligoarthritis, polyarthritis (rheumatoid factor negative), polyarthritis (rheumatoid factor positive), psoriatic arthritis, enthesitis related arthritis and undifferentiated arthritis.
Since then increasing evidence has accumulated suggesting that some of these categories are heterogeneous. Therefore, there is a need to revise the criteria in order to identify more homogeneous entities and to try to distinguish those diseases, if any, that are observed only in children from those that represent the childhood counterpart of adult diseases.
Differently from the ILAR classification, which was not formally validated but essentially developed by consensus, the aim of this study is to test the new proposed classification in a prospective collection of at least 1,000 patients at disease onset.

Data collection
The project includes the enrollment of a prospective cohort of at least 1,000 JIA patients, evaluated at onset and at 4 times points since the disease onset (within the first and after at least 3 months the second and then at least annually up to year 5). Related biologic samples will be collected at the first 2 time points (ANA, anti CCP, RF, HLA B27). The left over of the HLA B27 samples will be used for additional genetic analysis providing the family/patient consent/assent and additional approval by the ethics committee (if needed).

Inclusion criteria for the patients to be collected prospectively
The patients to be included in the prospective data collection must fit the following inclusion criteria:A diagnosis of JIA according to the ILAR criteria by the treating physician.

1. The availability to provide an evaluation within 6 months after the onset of JIA. The onset evaluation can also be completed retrospectively (based on reliable family history or prior attending physician's reports), but only if joint assessment data can be provided.
2. A clinical evaluation 3 months apart and then at least annually up to year 5.
3. The availability to centrifuge and collect samples.

The PRINTO coordinating centre will take care of the Ethics Committee procedure for the participating centres.
This project is funded by the Italian Ministry of Health.

STARS

The comparison of STep-up and step-down therapeutic strategies in childhood ARthritiS trial (STARS) is a new interventional trial

financed by AIFA (Agenzia Italiana del Farmaco) and by the Italian Foundation Compagnia di San Paolo that will be conducted by PRINTO only in the Italian centres. This clinical trial has the aim to investigate whether an early aggressive therapeutic intervention in children with JIA, based on the initial start of synthetic and biologic DMARDs (Step-down strategy), is superior to an approach based on treatment escalation conducted following the treat-to-target principle (Step-up strategy). The effectiveness of the two strategies will be assessed by comparing their ability to induce sustained clinical disease remission on/off treatment.
After screening of inclusion and exclusion criteria and recording of informed consent, patients will be randomized into two therapeutic arms: “Step up” or “Step down”. Patients in the Step-up arm will be treated according to a conventional strategy based on treatment escalation and driven by the treat-to-target strategy. Patients in the Step-Down arm will be treated with an early, combined, aggressive therapy for 6 months.

Rationale
The primary goal of the trial is to reach a sustained and complete disease quiescence. The achievement of such state implies the disappearance of joint pain, morning stiffness and functional limitation. This objective may lead to restoration of the ability of the child to make the activities of daily living and to improve the quality of life of the child and the family. Continued suppression of the inflammatory disease process may also help prevent long-term joint damage and, consequently, reduce the expenses of the health care system in terms of physiotherapy, need of devices (e.g. crutches, wheelchairs), orthopedic surgery, etc. The resulting reduced need of advanced therapies, particularly with biologic medications, that may be deserved in case of inadequate response to the conventional medications, may minimize the exposure of children to the potential side effects of long-term drug therapies and diminish the expenditures related to the administration of the costly biologic agents. Another potential advantage of the therapeutic regimens assessed in the trial is to avoid disease exacerbations, which may require the prescription of systemic corticosteroids. Minimizing the use of these medications may lessen the frequency of serious adverse events secondary to their prolonged administration, particularly growth failure, weight gain, and cushingoid features. Sustained disease control may also reduce the need of repeated corticosteroid joint injections, which cause distress to the child and the family and may increase the organizational and financial burden to the health care system in case of the need of general anesthesia in the operatory theatre. Broader objectives are the avoidance of absences of children from school and of parents from work, which may be caused by disease exacerbations or the request of frequent clinical visits or laboratory tests due to persistently active disease or continued treatment with potentially toxic medications. Particularly innovative aspects of the trial include the use of standardized quantitative measures to assess the disease state and the disease course over time and the involvement of patients and parents in clinical decision making, through their assessment of disease activity by child- or patient-centered outcome measures.

Objectives
The study is aimed to compare the effectiveness of a conventional therapeutic regimen, based on treatment escalation (Step-up strategy) and driven by the treat-to-target approach, with that of an early aggressive intervention based on a combination of conventional and biological DMARDs (Step-down strategy).
The hypothesis tested in this trial is whether an early aggressive therapy with a 6-month course of an anti-TNF agent in combination with methotrexate or with methotrexate alone in the milder forms of oligoarthritis (Step-down arm) is more effective in inducing clinical remission on medication (i.e. at least 6-month of continuous inactive disease while receiving anti-rheumatic medications) than a conventional therapeutic approach based on treatment escalation (Step-up arm), which efficacy is maximized through the implementation of a treat-to-target approach.

Primary endpoint
Clinical remission on or off medication at 12 months.
The effectiveness of the two therapeutic strategies will be compared by assessing the frequency of clinical remission (CR) at 12 months. CR is defined as the persistence of the JADAS state of ID for at least 6 months.
After the conclusion of the 12-month observation period of the trial, patients will be followed for up to 5 years for the evaluation of disease course, medication requirements, adverse events of medications, and long-term disease-related morbidity.
The trial will enroll newly-diagnosed and DMARD-naïve children with a diagnosis of oligoarthritis or rheumatoid factor negative polyarthritis according to the ILAR criteria.
The desired sample size for the study is 260 patients. Enrollment will start as soon as Ethics Committee approvals are obtained. The PRINTO coordinating centre will offer assistance during the process of the Ethics Committees submission.

All PRINTO Italian centres have been recently invited to participate in this project with a dedicated survey in the past few months.

For any further information, please contact PRINTO at printo@gaslini.org

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PharmaChild

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). 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.

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)

Eurofever

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 main objective of the project has been the creation of a **registry of autoinflammatory diseases.**
Few years ago a section dedicated to Efficacy and Safety has been implemented and the registry is able to collect also longitudinal information. Up to date **4126 patients** have been enrolled in the Registry **from 113 centers in 41 countries** and enrollment is ongoing.

Conect4children (c4c)

PRINTO is partner of the "conect4children" (c4c) initiative ; the collaborative network for European clinical trials for children, (c4c) is **a consortium that aims to enhance the competitiveness of Europe as a critical region for developing medicines for children by using existing expertise** , patient access and developing common processes to be applied to disease natural history studies, registries, studies of new therapies and comparisons of existing therapies.**The consortium is a novel collaboration between academic and private sectors that includes 33 academic and 10 industry partners from 20 European countries, more than 50 third parties and around 500 affiliated partners** .The six-year project, comprised of a multidisciplinary public-private consortium, brings together key stakeholders across academia and industry. It is a pioneering opportunity to build capacity for the management of multinational paediatric clinical trials across Europe whilst ensuring the voices of children, young people and their families are heard. Strong links with regulators will be established.
For more information you can click on the following link https://conect4children.org/

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 investigates the comparative efficacy and safety of MMF (experimental treatment) vs CYC (standard treatment) for induction of remission of childhood PAN. This is **the first ever randomized trial for childhood PAN.** The enrollment period has been officially closed on June 30th, 2018.

Patients enrolled in the PRINTO projects

Country	PHARMACHILD	EUROFEVER	Country	PHARMACHILD	EUROFEVER
Argentina	123	57	Japan	0	6
Armenia	0	101	Latvia	259	6
Australia	0	13	Lebanon	0	1
Austria	30	32	Lithuania	320	7
Belgium	0	13	Mexico	85	0
Brazil	398	17	Netherlands	695	132
Bulgaria	57	5	Norway	361	0
Canada	0	38	Oman	16	6
Chile	0	5	Poland	29	9
China	0	14	Romania	426	46
Croatia	186	14	Russian Federation	468	64

Czech Republic	120	215	Saudi Arabia	70	39
Denmark	542	135	Serbia	276	5
Ecuador	25	1	Slovakia	126	1
France	312	287	Slovenia	53	18
Georgia	0	9	Spain	717	255
Germany	1	303	Sweden	0	1
Greece	486	168	Switzerland	490	102
Hungary	128	24	Turkey	1	255
India	119	3	United Kingdom	0	296
Israel	89	168	United States	0	6
Italy	1611	1252	**Total**	**8619**	**4129**

PRINTO overall enrollment status

Latest PRINTO papers

Brunner HI, Tzaribachev N, Vega-Cornejo G, Louw I, Berman A, Calvo Penadés I, Antón J, Ávila-Zapata F, Cuttica R, Horneff G, Foeldvari I, Keltsev V, Kingsbury DJ, Viola DO, Joos R, Lauwerys B, Paz Gastañaga ME, Rama ME, Wouters C, Bohnsack J, Breedt J, Fischbach M, Lutz T, Minden K, Miraval T, Ally MM, Rubio-Pérez N, Solau Gervais E, van Zyl R, Li X, Nys M, Wong R, Banerjee S, Lovell DJ, Martini A, Ruperto N; Paediatric Rheumatology International Trials Organisation(PRINTO) and the Pediatric Rheumatology Collaborative Study Group (PRCSG).

Subcutaneous Abatacept in Patients With Polyarticular-Course Juvenile Idiopathic Arthritis: Results From a Phase III Open-Label Study.

Arthritis Rheum 2018 Jul;70(7):1144-1154 PubMed

Brunner HI, Holland M, Beresford MW, Ardoin SP, Appenzeller S, Silva CA, Flores F, Goilav B, Wenderfer SE, Levy DM, Ravelli A, Khunchandani R, Avcin T, Klein-Gitelman MS, Feldman BM, Ruperto N, Ying J, for the PRCSG and PRINTO Investigators

American College of Rheumatology Provisional Criteria for Global Flares in Childhood-Onset Systemic Lupus Erythematosus

Arthritis Care Res 2018 Jun;70(6):813-822 PubMed

Bharucha KN, Brunner HI, Calvo Penadés I, Nikishina I, Rubio-Pérez N, Oliveira S, Kobusinska K, Schmeling H, Sztajnbok F, Weller-Heinemann F, Zholobova E, Zulian F, Allen R, Chaitow J, Frane J, Wells C, Ruperto N, De Benedetti F; for the Paediatric Rheumatology International Trials Organisation and the Pediatric Rheumatology Collaborative Study Group .

Growth During Tocilizumab Therapy for Polyarticular-course Juvenile Idiopathic Arthritis: 2-year Data from a Phase III Clinical Trial

J Rheumatol 2018;45 (8) 1173-1179 PubMed

Sherman G, Nemet D, Moshe V, Consolaro A, Ravelli A, Ruperto N, Uziel Y for the Paediatric Rheumatology International Trials Organisation (PRINTO)

Disease activity, overweight, physical activity and screen time in a cohort of patients with juvenile idiopathic arthritis

Clin Exp Rheumatol. [Epub ahead of print] PubMed

Ben-Chetrit E, Gattorno M, Gul A, Kastner DL, Lachmann HJ, Touitou I, Ruperto N for the Paediatric Rheumatology International Trials Organisation (PRINTO) and the AIDs Delphi study participants

Consensus proposal for taxonomy and definition of the autoinflammatory diseases (AIDs): a Delphi study

Ann Rheum Dis [Epub ahead of print] PubMed

Holland MJ, Beresford MW, Feldman BM, Huggins J, Norambuena X, Silva CA, Susic G, Sztajnbok F, Uziel Y, Appenzeller S, Ardoin SP, Avcin T, Flores F, Goilav B, Khubchandani R, Klein-Gitelman M, Levy D, Ravelli A, Wenderfer SE, Ying J, Ruperto N, Brunner HI; for Paediatric Rheumatology International Trials Organisation and the Pediatric Rheumatology Collaborative Study Group (PRCSG)

Measuring Disease Damage and its Severity in Childhood-Onset Systemic Lupus Erythematosus.

Arthritis Care Res 2018 Feb 6, [Epub ahead of print] PubMed

PRINTO membership

As of today, PRINTO has reached 1349 effective members in 641 centres from 88 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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