Network in pediatric rheumatology: the example of the Pediatric Rheumatology International Trials Organization

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Background: **Pediatric rheumatic diseases (PRDs) are rare conditions associated with significant sequelae affecting the quality of life and long-term outcome. The research aimed at studying new therapeutic approaches is difficult because of logistic, methodological and ethical problems.**

Data sources: **To address these problems, two international networks, the Pediatric Rheumatology Collaborative Study Group (PRCSG) and the Pediatric Rheumatology International Trials Organization (PRINTO) were established. The two networks share the goal to promote, facilitate and conduct high quality research for PRDs.**

Results: **The PRINTO and PRCSG networks have standardized the evaluation of response to therapy in juvenile idiopathic arthritis (JIA), juvenile systemic lupus erythematosus, and juvenile dermatomyositis, drafted clinical remission criteria in JIA, and provided cross-cultural adapted and validated quality of life instruments including the Childhood Health Assessment Questionnaire and the Child Health Questionnaire into 32 different languages. In this paper we reviewed how the networks of the PRINTO and PRCSG have created the basic premises for the best future assessment of PRDs.**

Conclusions: **The PRINTO and PRCSG networks can be regarded as a model for international cooperation or collaboration in other pediatric subspecialties.**

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Introduction

Pediatric rheumatic diseases (PRDs) are rare conditions associated with significant morbidity, consequence on the quality of life, and monetary costs. Recent studies demonstrated that studies of the impact and outcome of PRDs have shown that this group of diseases is associated with greater morbidity and monetary cost than previously thought.[1] For example, long-term outcome studies of children with juvenile idiopathic arthritis (JIA) report that, after a mean follow-up of 15 years, the majority of the patients continue to experience some difficulties in daily living activities, and that moderate to severe pain is still present in 30% of the patients.[2-4] There is also evidence of cumulative organ damage in patients with juvenile systemic lupus erythematosus (JSLE).[5]

Certainly childhood chronic illnesses with high levels of morbidity should be the target of intense research aimed at ameliorating and/or curing the disease. However, conducting clinical trials in PRDs has proven difficult for a host of reasons. Due to the low prevalence of the diseases, the only possibility to gather a sufficient number of patients to obtain clinically and statistically valid results in a reasonable period of time, is to perform multi-center studies on an international scale. The ethics of conducting any placebo-controlled trial, even in adults, has recently come under intense scrutiny.[6-8] Parents often refuse entry into studies because they are uncomfortable with the prospect of their child being assigned by chance to a placebo group. Securing funding for conducting clinical trials in PRDs has always been difficult since the pharmaceutical industry has little interest in funding these trials due to the small potential market.

Drugs available for the treatment of PRDs have been used in new dosages, new routes of administration, and new combinations. Unfortunately, data regarding the safety and effectiveness of these new treatment regimens tend to be from small, open, anecdotal, uncontrolled, non-randomized case series. Examples include the use of high dose MTX in recalcitrant JIA[9,10] and MTX usage in juvenile dermatomyositis.[11] Many of these new approaches to

management may represent improvements over existing standards, but without larger, systematic trials the data will remain statistically unproven.

The history of collaborative research in pediatric rheumatology

The Pediatric Rheumatology Collaborative Study Group (PRCSG at *www.prcsg.org*)

Founded in 1973 by Dr Earl Brewer and led in the following years by Drs. Edward H. Giannini and Daniel J. Lovell, the purpose of the PRCSG is to foster, facilitate, and conduct high quality research in the field of pediatric rheumatology in North America. The activities of the PRCSG are governed by written bylaws and oversight and long range planning is provided by the PRCSG Advisory Council. The PRCSG Coordinating Center is located in Cincinnati, Ohio, USA.

The main focus of the PRCSG in its early years was related to clinical trials of non-steroidal anti-inflammatory drugs (NSAIDs) in JIA.[12] Their pioneering methodological groundwork for the conduct of clinical trials[13-17] set the basis for the further development of evidence-based collaborative research in PRDs. The PRCSG started the work in the field of disease modifying anti-rheumatic drugs (DMARDs),[18] which led to the demonstration of the ineffectiveness of penicillamine, hydroxychloroquine[19] and auronafin[20] in the treatment of severe JIA. It should be noted that to reach an adequate sample size for the above mentioned trials it was necessary to establish an international collaboration between the United States and the former Soviet Union.

Their seminal work resulted in a significant change in the current clinical practice of the pediatric rheumatology community especially after the publication of the methotrexate (MTX) trial[21] in JIA, which demonstrated the efficacy of this drug at the dosage of 10 mg/m^2 per week. Since 1992 MTX indeed has become the drug of first choice for the treatment of JIA patients whose disease is resistant to NSAIDs.

The PRCSG more recently developed, in collaboration with the Food and Drug Administration (FDA), a new study design called randomized withdrawal design. According to this design children are first treated in an open fashion with the active drug and then the responders are randomised in a double blind fashion to be switched to placebo or continue with the active drug. This design has been accepted by regulatory agencies throughout the world as the standard study design for use in evaluation of new therapies for children with JIA. This study design has been successfully used by the PRSCG in performing the first trial of a biologic therapy in JIA.[22]

The Pediatric Rheumatology International Trials Organization (PRINTO at *www.printo.it* or *www.pediatric-rheumatology.printo.it*)

The PRINTO founded by Alberto Martini and Nicolino Ruperto in 1996 initially included 14 European countries (now more than 50 countries with more than 250 centers world wide) with the idea to perform clinical trials for the PRDs with or without the support of pharmaceutical companies.[23,24] The PRINTO aims to facilitate and coordinate the development, conduct, analysis, and reporting of clinical trials and outcome assessment standardization in children with PRDs. In general, if a study is not supported by a pharmaceutical company the design is a randomized, actively controlled, and open label clinical trial. If the study is supported by a pharmaceutical company and is part of a clinical development program which aims at marketing an agent, more classic designs are used.

Composed of academic, clinical centers actively engaged in the research/clinical care of children with PRD, the PRINTO actually has the most esteemed pediatric rheumatology researchers outside the USA. It has four main vertical structures: the Advisory Council that provides leadership and guidance for PRINTO research activities; the International Coordinating Center whose main task is to facilitate the flow of logistic and scientific details needed to design, launch and manage multi-centered, multi-national, collaborative studies; the National Coordinating Centers (one per country) whose tasks are to facilitate the participation of the greatest number of individual centers, and to provide the translation of all the forms to be completed by the parents/patients; and finally the individual clinical sites that constitute the main support structure to obtain a critical mass of data for on-going and future research.

In recent years, the PRINTO and the PRCSG have worked closely in various international collaborative projects detailed below.

How to define response to treatment in JIA

Until the late 1990s, the assessment of clinical response in JIA was not standardized. Multiple measures of outcome were in use and different trials used different endpoints. Some of these endpoints had low validity characteristics and were insensitive to change, some were redundant, and some were non-reliable (poor reproducibility). Additionally, there was little consensus on the amount of change in endpoints which signifies clinically important improvement or worsening. This lack of standardization led to inefficient trials

that required larger than necessary sample size, an increased risk of statistical error, possible reporting bias, multiple or ambiguous interpretations of the results, and an inability to compare multiple therapies using meta-analysis techniques.

The main aim of this first combined effort made by the PRCSG and PRINTO under the guidance of Dr EH Giannini was to develop a standardized core set of measures and a definition of improvement for the evaluation of response to therapy in JIA that would be accepted by the international community.

There are 6 validated outcome measures in the JIA core set[25,26] that measure different domains of disease activity: the number of joints with active arthritis, the number of joints with limited range of motion; the physician global evaluation of disease activity; the parent assessment of child's overall well-being; a functional assessment tool; and the westergren erythrocyte sedimentation rate (ESR). A patient must demonstrate at least 30% improvement from baseline in at least 3 of any 6 JIA core set variables with no more than 1 of the remaining variables worsened by more than 30% is classified as improved. The definition of improvement allows researchers and clinicians to dichotomize patients into responders or non-responders.

After its publication,[26] the definition of improvement was adopted by the FDA as the primary outcome for all clinical trials involving children with JIA, and subsequently officially recognized by the American College of Rheumatology (ACR) and renamed the ACR Pediatric 30.[27]

The methotrexate trial in JIA

After the trial published by Giannini et al[21] methotrexate became the disease-modifying-agent of first choice in polyarticular course JIA. For children who did not respond to 10 mg/m^2 per week it became a common practice to use a higher dose of MTX, up to 30 mg/m^2 per week,[10] but no randomized trial had confirmed this practice. Knowledge of the optimal dosage of MTX in term of efficacy and safety is central to disease management, the PRINTO, supported by the European Union (Contract BMH4 983531), conducted a randomized, open label standard-of-care trial to evaluate the MTX efficacy and safety profile in an intermediate versus a higher dose of MTX for the treatment of polyarticular course JIA patients who failed to improve on a standard dose of MTX. The trial showed that the plateau of efficacy of MTX in JIA was reached with the parenteral administration of 15 mg/m^2 per week and that further increase in dosage was not associated with any additional therapeutic benefit.[28]

From a methodological point of view, the trial was built on the current "standard of care" in such a way that the cost of insurance coverage, medication, clinic visits, and laboratory monitoring, were paid by the usual method of cost reimbursement for clinical care in each participating country. The amount of data collected, in addition to that from routine follow-up, was minimal, and all investigators volunteered their time and effort. The study received no support from pharmaceutical industry.

The next steps were to launch clinical trials in Europe and to prepare standardized tools for the outcome assessment of children with PRD to be used internationally among nations with different languages and cultures.

The quality of life project for PRDs

One particular problem when conducting international trials was the availability of parent's/patient's reported outcome for functional ability and quality of life assessment. Thanks to the European Union (Contract BMH4 983531), the PRINTO has been able to cross-culturally adapt and validate 2 questionnaires: the Childhood Health Assessment Questionnaire (CHAQ) for functional ability assessment in JIA and juvenile dermatomyositis (JDM), and the Child Health Questionnaire (CHQ) for health related quality of life evaluation for all PRDs. The project enrolled 6644 subjects (3235 patients with JIA and 3409 healthy children), with 32 validated versions of the CHAQ and CHQ now available.[29-31] The CHAQ is now the functional assessment tool used for nearly all trials in JIA,[22,28] and the CHQ for quality of life assessment papers.[32-35]

Disease activity and damage assessment in JSLE and JDM

Once the problem of a standardized approach for the evaluation of response to therapy in JIA was resolved, the logical follow-up study was to conduct a similar project for 2 other chronic PRDs, JSLE and JDM. With a second grant from the European Union (contract n^o QLG1-CT-2000-00514) the PRINTO, in collaboration in the PRCSG, has been able to propose validated core sets for the evaluation of disease activity and damage[36-38] and also definitions of improvement to be used in future clinical trials in JSLE[39] and JDM (paper in preparation). A total of 295 patients with JDM and 556 patients with JSLE were collected from 41 countries. These projects have been officially endorsed by the ACR and the European League Against Rheumatism (EULAR) and are now known as the PRINTO core set[37] and the PRINTO/ACR definition of

improvement for JSLE[39] and PRINTO/ACR/EULAR core set for JDM.[38]

A website for families of children with pediatric rheumatic diseases

Although collaborative research is usually set up with the objective to answer specific scientific questions, the social aspect of research needs to be taken into account, and the needs of the parents. The availability of the Internet allows families to access medical information quickly and easily, but this information is often not standardized, inaccurate and unreliable. To address this problem, the PRINTO in collaboration with the Pediatric Rheumatology European Society (PRES), supported by the European Union (contract 2001CVG4-808), has recently finished a project with the goal to prepare a website for families and health professionals, containing consensus defined information about PRDs (in the format of frequently answered questions), the list of pediatric rheumatology centers, and the list of family help associations. All information is available and has been translated into the languages of the countries belonging to the PRINTO network (*www.pediatric-rheumatology.printo.it*).[40]

Research training in pediatric rheumatology

Good collaborative clinical research requires qualified people around the world to conduct studies in a standardized fashion.[41] The PRINTO, with another grant from the European Union (Contract no AML/B7-311/97/0666/II-0246-FI), has set up a research training program in pediatric rheumatology to support mainly Latin America recipients (Argentina, Brazil, Chile, Costa Rica, Cuba, or Mexico). The 24 Latin American recipients will attend a course in Genoa, Paris, Utrecth, Goteborg and London. The project will also allow 4 trained pediatric rheumatology fellows from Genoa, Italy to spend several months in Latin America (Buenos Aires in Argentina, Rio de Janeiro and Botucatu in Brasil, Mexico City in Mexico) to standardize the outcome assessment of patients participating in common collaborative studies.[5,33-35,42-46]

The clinical remission criteria for JIA

Recently, the PRINTO and PRCSG are working with the recently founded Childhood Arthritis and Rheumatology Research Alliance (CARRA) to develop draft criteria for inactive disease and clinical remission for each subtype of JIA categories.

The criteria considered for inactive disease include: no active arthritis; no fever, rash, serositis, splenomegaly, generalized lymphadenopathy attributable to JIA; no active uveitis; normal erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP); and a physician's global assessment of disease activity rated at the best score possible for the instrument used. Six continuous months of inactive disease define clinical remission on medication, while 12 months off medication define clinical remission off medication.[47]

The pediatric rule

Most, if not all of the PRD drugs are used "off label" in most countries worldwide, meaning that no indication for pediatric use is printed on the drug label.[48-50]

The paucity of controlled trials in childhood prompted the passage of legislation that gives regulatory authorities such as the FDA[49] (the Pediatric rule recently renewed until 2012), and more recently by the European Union[51] the power to require pharmaceutical sponsors to perform and support trials of new agents in children. As a result of such US and EU legislation, several clinical trials supported entirely by pharmaceutical industries have been completed in children with JIA.[22,52-54] Others are currently running very effectively and others are in development.

Conclusions

The creation of big international trial networks such as the PRINTO and PRCSG, the definition of internationally recognized and standardized outcome measures and definitions of improvement for JIA, JSLE and JDM, the cross-cultural adaptation and validation of quality of life instruments, and the adoption of adequate legislative measures (pediatric rule) created the framework for the optimal future assessment of the efficacy of new treatments for PRDs. With the guiding principles, children with rheumatic diseases now have the same rights as adults to be treated with drugs whose safety and efficacy have been assessed. The PRINTO and PRCSG networks can be seen as a model for international cooperation or collaboration in other pediatric subspecialties.

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