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МЕДИЦИНСКИЕ НОВОСТИ ГРУЗИИ

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SUMMARY

NEW APPROACH TO ESTIMATE DIFFERENT DRUGS AND/OR OTHER MEDICAL INTERVENTIONS EFFECTIVENESS BASED ON FUZZY LOGIC PRINCIPLES

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A new approach for the evaluation of the efficacy of drugs and/or other medical interventions is proposed. It is based on the principles of fuzzy logic, particularly on fuzzy sets, fuzzy cluster analysis and fuzzy expert system.

Key words: drugs, medical interventions, fuzzy logic.

РЕЗЮМЕ

НОВЫЕ ПОДХОДЫ ДЛЯ ОПРЕДЕЛЕНИЯ ЭФФЕКТИВНОСТИ ЛЕКАРСТВ И/ИЛИ ДРУГИХ МЕДИЦИНСКИХ ВМЕШАТЕЛЬСТВ С ИСПОЛЬЗОВАНИЕМ ПРИНЦИПОВ НЕЧЕТКОЙ ЛОГИКИ

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Предлагается новый подход для оценки эффективности лекарств и/или других медицинских вмешательств. Он основывается на принципах нечеткой логики, в частности, нечетких множеств, нечеткого кластерного анализа и нечеткой экспертной системы.

NETWORK IN PEDIATRIC RHEUMATOLOGY: THE EXAMPLE OF THE PEDIATRIC RHEUMATOLOGY INTERNATIONAL TRIALS ORGANISATION

Ruperto N, Martini A for the Paediatric Rheumatology International Trials Organisation (PRINTO)

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The pediatric rheumatic diseases (PRD) are rare conditions associated with substantial morbidity, consequence on the quality of life, and monetary costs. Many studies of the impact and outcome of PRD 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 PRD has proven difficult for a host of reasons.

Due to the rarity 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-centre studies on an international scale. The ethics of conducting any placebo-controlled trial, even in adults, has recently come under intense debate [6-8]. Parents often refuse entry into studies because they are uncomfortable with the prospect of their child being assigned by chance to placebo. Securing funding for conducting clinical trials in PRD 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 PRD 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 tends 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 of 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 must remain suspect.

The history of collaborative research in pediatric rheumatology.

The Pediatric Rheumatology Collaborative Study Group (PRCSG).

Founded in 1973 by Dr Earl Brewer and lead 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 (NSAID) in juvenile rheumatoid arthritis (JRA) [12.]

Their pioneering methodological works for the conduct of clinical trials (13-17) set the basis for the further development of evidence-based collaborative research in PRD.

Indeed, in the ensuing years the PRCSG started the work in the field of disease modifying anti rheumatic drugs (DMARDs) [18] that lead to the demonstration of the ineffectiveness of penicillamine, hydroxychloroquine [19] and auronafin [20] in the treatment of severe JRA. 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 lead to a significant impact in the current clinical practice of the pediatric rheumatology community, especially after the publication of the methotrexate (MTX) trial [21] in JRA, that demonstrated the efficacy of this drug at the dosage of 10 mg/m²/week. Since 1992 MTX indeed has become the drug of first choice for the treatment of JRA patients whose disease is resistant to NSAIDs.

The PRCSG more recently developed a randomized withdrawal study design in collaboration with the Food and Drug Administration (FDA) that has been accepted by regulatory agencies throughout the world as an acceptable study design for use in evaluation of new therapies for children with JIA. This study design was succefully used by the PRSCG in performing the first trial of a biologic therapy in JIA [22].

The Pediatric Rheumatology International Trials Organisation (PRINTO).

The Pediatric Rheumatology International Trials Organization (PRINTO) was founded by Alberto Martini and Nicolino Ruperto in 1996, and initially included 14 European countries (now more countries with more than 250 centres world wide) [23,24]. PRINTO aims are to facilitate and co-ordinate the development, conduct, analysis, and reporting of clinical trials and outcome assessment standardization in children with PRD. PRINTO was founded with the idea to perform clinical trials for the PRD with or without the support of pharmaceutical companies. In general, if a study is not supported by a pharmaceutical company the design is that of 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 for marketing an agent, more classic design are used.

PRINTO is composed of academic, clinical centers actively engaged in the research/clinical care of children with PRD. PRINTO actually is composed of the most esteemed pediatric rheumatology researchers outside the US. PRINTO has four main vertical structures: the Advisory Council that provide leadership and guidance for PRINTO research activities; the International Coordinating Centre whose main task it to facilitate the flow of logistic and scientific details needed to design, launch and manage multi-centered, multi-national, collaborative studies; the National Coordinating Centres (one per country) whose tasks are to facilitate the participation of the greatest number possible 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.

The ACR pediatric 30 definition of improvement for JIA. Up until the late 1990's, the assessment of clinical response in JIA/JRA 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 about 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 sizes, 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-analytic techniques.

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

There are 6 validated outcomes measures in the JIA core set [25,26] that measures 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; the Westergren erythrocyte sedimentation rate (ESR). To be classified as improved 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%. 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/m²/week it became common practice to use higher dose MTX, up to 30 mg/m²/week (10), but no randomized trial had confirmed this hypothesis. Knowledge of the optimal dosage of MTX in term of efficacy and safety is central to disease management, 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 intermediate versus higher dose for polyarticular course JIA patients who failed to improve on standard dose MTX. The trial shows that the plateau of efficacy of MTX in JIA is reached with the parenteral administration of 15 mg/m²/week and that further increase in dosage is 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, the 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 pharmaceutical industry support.

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 PRD.
One particular problem for the conduct of international studies 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) 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 6,644 subjects (3,235 patients with JIA and 3,409 healthy children), with 32 validated version 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° QLG1-CT-2000-00514) PRINTO, with collaboration with 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 project have been officially endorsed by the ACR and the European League Against Rheumatism (EULAR) and are now know as PRINTO core set (37) and 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.
Collaborative research is usually set up with the objective to answer specific scientific questions but also the social aspect of research has to be taken into account, and in particular the needs of the parents. The actual large availability of the use of the internet allows families to access medical information quickly and easily, but this informa-

tion is often not standardized, inaccurate and unreliable. To address this problem, PRINTO in collaboration with the Paediatric Rheumatology European Society (PRES), and again supported by the European Union (contract 2001CVG4-808) has recently finished a project with the goal to prepare a website, directed to families and health professionals, containing consensus defined information about PRD (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 all the countries belonging to the PRINTO network (www.pediatric-rheumatology.printo.it) (40).

Research Training in paediatric rheumatology.
Good collaborative clinical research requires qualified people around the world able to conduct studies in a standardized fashion (41). PRINTO, with another grant from the European Union (Contract no AML/B7-311/97/0666/II-0246-FI), has set up a research training programme in pediatric rheumatology, to support mainly Latin America recipients (Argentina, Brazil, Chile, Costa Rica, Cuba, or Mexico). For the 24 Latin American recipients the course will take place in Genoa in Italy, Paris in France, Utrecth in the Netherlands, Goteborg in Sweden, and London in United Kingdom. The project will also allow 4 trained pediatric rheumatology fellows from Genoa, Italy to spend some months in Latin America (Buenos Aires in Argentina, Rio de Janeiro and Botucatu in Brasil, Mexico City in Mexico) to standardise the outcome assessment of patients participating to common collaborative studies [5,33-36,42-46].

The clinical remission criteria for JIA.
In the last years PRINTO and PRCSG have worked with the North America recently founded Childhood Arthritis and Rheumatology Research Alliance (CARRA), in order to develop draft criteria for inactive disease and clinical remission for select JIA categories.

Draft criteria for inactive disease include: no active arthritis; no fever, rash, serositis, splenomegaly, generalized lymphadenopathy attributable to JIA; no active uveitis; normal 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 reported on the drug label [48-50].

The paucity of controlled trials in childhood prompted passage of legislation that gives regulatory authorities such as the Food and Drug Administration (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 JRA [22,52-54], others are currently running very effectively and others are in development.

The creation of big international trial networks such as 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, the adoption of adequate legislative measures (pediatric rule), have created the basic premises for the best future assessment of the efficacy of new treatments for the PRD. Therefore, children with rheumatic diseases now have the same rights of adults to be treated with drugs whose safety and efficacy have been assessed.

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SUMMARY

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The pediatric rheumatic diseases (PRD) are rare conditions associated with important sequelae on 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.

To face these problems 2 international networks; the Pediatric Rheumatology Collaborative Study Group (PRCSG) and the Paediatric Rheumatology International Trials Organization (PRINTO) have been founded. The 2 networks have the goal to promote, facilitate and conduct high quality research for the PRD. In particular they have been able to standardize the evaluation of response to therapy in juvenile idiopathic arthritis (JIA), juvenile systemic lupus erythematosus, and juvenile dermatomyositis, to draft clinical remission criteria in JIA, and to provide cross-cultural adapted and validated quality of life instruments like the Childhood Health Assessment Questionnaire, and the Child Health Questionnaire, into 32 different languages.

In this paper we reviewed how the creation of large international trial networks such as PRINTO and PRCSG, the definition of internationally recognized and standardized outcome measures and definitions of improvement, the validation of quality of life instruments, the adoption of adequate legislative measures (pediatric rule), have created the basic premises for the best future assessment of the PRD. This progress now offers children with PRD the same opportunities as adults to be treated with drugs whose safety and efficacy have been assessed through legitimate scientifically valid investigations.

Key words: pediatric rheumatic diseases, quality of life.

РЕЗЮМЕ

ОРГАНИЗАЦИЯ ПО ПРОВЕДЕНИЮ МЕЖДУНАРОДНЫХ КЛИНИЧЕСКИХ ИССЛЕДОВАНИЙ В ОБЛАСТИ РЕВМАТОЛОГИИ

Руперто Н., Мартини А. для Организация по проведению международных клинических исследований в области педиатрической ревматологии (PRINTO)

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Педиатрические ревматические болезни (ПРБ) являются редкими состояниями, обусловливающими тяжелые неже-