

Report from the PReS Meeting in Versailles, France Sept 2005 Clinical Presentations: Clinical study group and PRINTO reports

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I PRINTO REPORT

A. *Planned PRINTO prospective JDM study-Ruperto and Ravelli (Genoa)*

1. 5 year trial
2. Objective: Determine which treatment regimen is associated with the lowest occurrence of flares and toxicities.
3. Prednisone alone versus prednisone + cyclosporine versus prednisone + methotrexate
4. Muscle biopsy at diagnosis will be optional.
5. Treatment protocol:
 - a. 3 days pulse of methylprednisolone at 30 mg/kg/day
 - b. Randomize patients to prednisone alone versus prednisone with cyclosporine (up to 5 mg/kg/day) versus prednisone + weekly methotrexate.
 - c. Prednisone use will be formalized and regimented with full dose for the first month with prednisone taper over the next 5 months at 0.2 mg/kg/day. Then in next 18 months prednisone will be lowered stepwise to 0.1 mg/kg/day. Each center will use the same tapering schedule.
 - d. Response measures will include:
 - 1.) Time to response of 25%, 50%, 75% improvement in first six months.
 - 2.) Time to clinical remission or time to flares from 6-24 months.
 - 3.) MD global assessment
 - 4.) Muscle strength assessment
 - e. Improvement criteria to be used.
 - f. Exclusion criteria, e.g., low neutrophils, GI ulceration, pulmonary disease or hemorrhage

C. *PRINTO cyclophosphamide study for SLE nephritis with different drug combinations-Ruperto and Ravelli (Genoa).*

1. Eighty centers willing to participate with 1-3 patients each.
2. Three 6 month therapeutic regimens for newly diagnosed severe SLE nephritis each beginning with a 3 day methylprednisolone pulse at 30 mg/kg/day.
 - a. 1st group: oral Cytoxan daily 1-2 mg/kg/day prednisone (cyclophosphamide exposure 180 mg/kg).
 - b. 2nd group: oral prednisone plus cyclophosphamide with European style pulses every 15 days at 500 mg/m² (exposure 108 mg/kg)
 - c. Prednisone + 7 monthly NIH pulses at 1000 mg/m² (exposure 120 mg/kg).
 - d. All three groups put on azathioprine plus prednisone after 6 months.
3. Inclusion criteria
 - a. Newly diagnosed child with severe SLE nephritis proved by biopsy.
4. Exclusions-e.g.
 - a. Previous cyclophosphamide
 - b. Leukopenia, neutropenia
 - c. Compliance problems
5. Use SLE PRINTO tools for measuring outcome

- a. Improvement: 2/5 measures improved at 50% or more and with no more than 1/5 worsening by 50% or more.
- 6. Data collection thru website www.printo.it and final version free by e-mail.
- 7. No financial support yet.

D. PRINTO prospective, randomized trial evaluating the optimal way to utilize methotrexate during clinical remission of JIA. Ruperto and Ravelli (Genoa)

Question: How long to continue methotrexate once clinical remission is achieved? It's believed that 50% of children with JIA do relapse after methotrexate is stopped. Relapses also appear to be independent of the duration of treatment with mtx

1. Protocol
 - a. Group A methotrexate is stopped at 6 months after clinical remission achieved.
 - b. Group B methotrexate is stopped at 12 months.
 - c. Patients are evaluated q 3 months for 1 year for a total of 9 visits.
 2. Criteria for remission
 - a. No systemic features for 3 months-no abnormal exam findings, no increased CRP/ESR
 - b. No recent intraarticular corticosteroids.
 - c. Low dose pred-NSAID ok
 3. Blood samples to be taken.
 4. Thus far 128 patients are entered from 70 centers (1/2 from London, Utrecht)
 5. One hundred Euro will be paid to each patient at the end of the study.
- E. Ongoing report on Infliximab study- (Other data presented last year)-Ruperto*
1. Initially would appear that fewer side effects with 3 mg/kg dose and many more SAE's with 6 mg/kg than 3 mg/kg by 19 to 5.
 2. Infusion reactions much higher in 3 mg than 6 mg 9.1 to 3.0
 3. Antibodies 3x more in 3 mg/kg than 6 mg/kg, antibody to infliximab-3 with high titers 1:20480; association possible between antibody titers and infusion reactions.
 4. No TB noted in first 52 weeks.
 5. Serious infections did occur, e.g., pneumonia.
 6. Efficacy profile the same between groups.
 7. Side effects overall good.
 8. 3 mg/kg group had more problems with infusion side effects though drug levels were as good as the 6 mg/kg group and PK's better.
 9. 6 mg/kg group has more total adverse events with no added efficacy.

II PReS Working Groups

- A. Lupus Working Group-Angelo Ravelli (Pavia)
 1. Lupus studies at PReS in coordination with PRINTO
 - a. Introduction

There has been a mild decrease number of scientific work among PReS members noted before this meeting. Several reasons may explain this trend:

- 1) There is difficulty of studying lupus in general.
- 2) Adult research in SLE may take priority in funding.
- 3) Adult research in SLE often includes adolescents.
- 4) Juvenile SLE has relatively low prevalence.

Most studies in the past have been retrospective and cross-sectional and few have used standardized definitions and outcome instruments. It is time to focus on prospective studies. We would like to begin a long term (60 months) prospective data collection via the internet as a SLE registry that will be coordinated by PRINTO.

b. Objectives of the new study as proposed:

- 1) To establish a multinational, multicenter study
- 2) To assess long term outcome of juvenile SLE
- 3) To describe clinical manifestations, lab, clinical course, treatment modalities and complications.
- 4) To assess impact on prognosis of the different treatment modalities currently utilized for SLE.
- 5) To identify early prognostic factors.

c. Inclusion criteria

- 1) Newly diagnosed patients under 18 years of age
- 2) SLE by ACR criteria (1992)
- 3) Study approved by the IRB and ethical board
- 4) Appropriate consents signed.

d. An internet based data sheet will be utilized for ease of use.

Below is a partial list of the data to be collected:

- 1) Demographic data:
Name or identification number, birth date, medical record number, demographic data, gender, date of first visit, physician's name, physician's city and country, disease onset type-acute or evolving, sociodemographic data
- 2) Presenting clinical manifestations:
 - a) Organ system, constitutional, cutaneous, msk, vascular, cardiac, and other organs
 - b) ACR criteria at time of diagnosis-11 criteria

e. Assessment of growth and development

- 1) Weight, height
- 2) Tanner Staging

f. Laboratory results to be documented;

- 1) CBC, ESR, CRP
- 2) Creatinine, urinalysis, 24 hour protein, creatinine clearance, C3, C4.
- 3) Serologies: ANA, Anti-DNA, ENA
- 4) Anti-cardiolipin, LAC
- 5) Other

g. Medications started at diagnosis:

- 1) NSAIDs
- 2) Corticosteroids (po and/or IV)
- 3) Hydroxychloroquine
- 4) Azathioprine
- 5) Mycophenolate
- 6) Methotrexate
- 7) Cyclophosphamide
- 8) Cyclosporine A
- 9) Other drugs,

h. Disease activity and outcome measures

- 1) SLEDAI-2K
- 2) Global assessment (VAS) by physician
- 3) Global assessment (VAS) by parent/patient
- 4) Child Health Questionnaire (CHQ) to be filled out by parent for the child

- i. Additional data to be collected every six months
 - 1) Major complications
 - 2) Mortality data including if cause of death, due to SLE
YES NO Unclear
 - 3) Drug therapy in the six months since last report including the drug, dose, route, dates of use
- j. Additional data to be collected every 12 months
 - 1) Growth and Development-height, weight, Tanner
 - 2) CHQ parent
 - 3) SLICC/ACR DI
 - 4) Global assessment of damage by the physician
 - 5) Global assessment of activity by parent

2. *Antiphospholipid syndrome registry-Tadej Avcin (London)*

A. Introduction

The International Registry for Pediatric Patients with the Antiphospholipid Syndrome was begun 1 ½ years ago at the European Phospholipid Meeting in London. The rationales included:

- 1. Though pediatric reports and studies have been unusual, it is believed that APLA problems are becoming more frequent in Europe.
- 2. There also are important differences from adults with APLA, e.g., effects of smoking and atherosclerosis.
- 3. There appear to be unique factors in children to evaluate, e.g.,
 - a. prevalence of specific disease manifestations
 - b. increased incidence of infection.
 - c. effects of long-term APLA therapy in kids

B. Objectives

- 1. Organize an international and European registry.
- 2. Study long term outcomes.

C. Organization

- 1. Collaboration of PRINTO and European Forum on antiphospholipid antibodies.
- 2. It will be an online, internet-based registry.
- 3. Confidentiality issues will be addressed.

D. Inclusion. Criteria

- 1. Diagnosis of APS before 18th year
- 2. Preliminary clinical criteria-vascular thrombosis; Lab criteria; anticardiolipin antibody of IgG and/or IgM (IgG and IgM medium to high positive) or positive lupus anticoagulant.

E. Study data sheet on internet

The data sheet included demographic data, disease related data (arterial, venous, small vessel thromboses, neurological diseases, hematological disorders, skin disorders, and other disorders). It also will include the APLA lab findings with the detection methods used as well as the SLE diagnostic assays utilized. The treatment and outcome data will also be collected.

Please e-mail Dr. Avcin if you are interested in participating in this study.

III JUVENILE DERMATOMYOSITIS (JDM) STUDY GROUP-C. Pikington (London)

Discussion topics

- A. IVIG study
- B. Muscle biopsy scoring project
- C. Allied health professionals report
- D. IMACS project + Rituximab study

- E. Criteria for DM diagnosis
- F. Classification of myopathies

A. IVIG

Survey of 50 studies-most centers start with steroids. IVIG only occasionally used. In discussions with members, it was agreed that an IVIG study appears to be too expensive. Plus there does not seem to be sufficient interest in what may be a difficult study. A study comparing cyclosporin A and methotrexate may be more pertinent. A pilot trial has been begun and contact Dr. Pilkington if you are interested.

B. Grading of muscle biopsies

There are few if any pediatric rheumatologists who are experts in interpreting muscle biopsies. So muscle histopathologists were needed. The pathologists were recruited from Europe and the USA. The goal of this muscle biopsy project was to develop a muscle biopsy scoring system which has never been done for JDM. To develop this scoring, it was necessary to convene a muscle biopsy consensus meeting. For this meeting, a cooperative retrospective, multicenter study of juvenile dermatomyositis patients who have had muscle biopsies was needed.

The initial Biopsy Consensus Conference was held in March 2005 in London. It took one day to agree upon a scoring system. The second day the scoring system was tried out on muscle biopsies. The pathologists were introduced to the VAS tool which they adjusted to. It turned out to be easy to agree upon whether a biopsy was technically acceptable but there was less agreement on the findings of each biopsy. The 2nd meeting of histopathologists is planned in March 2006. The study remains a work in progress. Funding is being provided by several UK myositis organizations.

C. Allied Health Professional report

A survey was performed on physical therapy (PT) interventions in early JDM-PT's in 19 countries-replied-50% had no PT intervention in active phase of JDMS-It is tentatively planned to repeat the study with more centers. A new survey will look at another part of PT intervention, the need for a fatigue assessment/measurement. This tool should be easy, practical, and quick. Eventually complementary core outcome measures for PT are needed that might fit well with the PRINTO JDM outcome measures

D. IMACS core study-Lisa Ryder and Daniel Eisenberg-multicenter study is ongoing.

1. JDM outcome measure is being tested that includes among others:
 - a. Physician global activity: 10 cm VAS
 - b. Patient or parent VAS
 - c. Manual muscle testing
 - d. Physical function-outcome
 - e. Laboratory tests

Definition of improvement is: 3/6 criteria improved by >20%

No more than 2 worse by >20% (not including the manual muscle testing)

2. Rituximab study at NIH

This is an international study involving both adult and childhood JDM. This study is limited to refractory patients with JDM. The dose will be 750 mg/m² at weeks 1 and 2. It includes two treatment groups.

Group A: Rituximab in week 1 and 2

Group B: Placebo infusions at weeks 1 and 2.

This group will receive Rituximab at 9 weeks.
Study Investigators had a meeting in Sept 2005, beginning patient recruitment in autumn 2005.

E. Criteria for diagnosis of JDM

Initial survey on diagnostic criteria was sent out to 110 centers. So far only 42 replies have been received, a 38 % response rate. Three criteria had wide agreement: muscle weakness, rash, and muscle enzyme elevation. There was little agreement after that, though the EMG and MRI tests were close to obtaining the necessary number of responses to be a criterion. There was interest in a formal study on criteria in the 41/42 centers that responded. Thirteen centers could provide all categories of cases-paper cases that are retrospective. Both JDM and overlap JDM diagnostic criteria would be analyzed. Brian Feldman in Toronto is coordinating this study. He is willing to collate and analyze the data. An internet data form will be used. No funding is available yet. Expect that an e-mail from Dr. Pilkington will sent out soon.

F. Classification study of JDM/overlap syndromes

There has been no past consensus on the meaning of JDM overlap syndromes. Now there is a huge and complicated effort on classification for JDM and other muscle diseases in adults and children that will address overlap as well as all myopathy categories. It will be a multispecialty consensus study including adult and pediatric neurologists as well as adult and pediatric rheumatologists. Classification will include inflammatory myositis, limb girdle dystrophies, fascioscapular dystrophy, drug toxin myopathy, infectious myopathy, and others. Funding is from the ACR and EULAR The next meeting will be in November 2005.

IV. RATIO registry organization

- A. French collaborative group includes internist and pediatric organization of rheumatologists, gastroenterologists, pulmonologists, infectious disease specialists, and general internists.
- B. The collaborative group surveys for side effects of TNF therapy in France especially for infections such as TB, Listeria, aspergillus, pneumocytis, and others.
- C. The group is particularly alert for lymphoma.
- D. Methods
 - 1. Prospective registry since February 2004
 - 2. Surveying for severe bacterial infections, opportunistic infections, and lymphoma.
 - 3. Participants included 474 centers in France.
 - 4. Mail was sent out with 4 reminders per yea.
 - 5. Reports made obligatory to govt
 - 6. Confirmed infection or lymphoma was checked thoroughly.
 - 7. When medicine was given is important, e.g., if medicine was given > 2 years ago, the infection is not counted. (Not so lymphoma)
 - 8. Three committees set up to review and verify validity of reports.
- E. Present results
 - 1. 137 cases of infection or malignancy
 - 2. Sixty infections were severe bacterial infections.
 - 3. Sixty-three infections were opportunistic.
 - 4. Thirteen lymphomas were noted.
 - 5. Only 2 children in the 137 cases
 - 6. The majority were adults with rheumatoid arthritis or spondyloarthritis
 - 7. Nineteen were on infliximab, 25 etanercept, 9 Humira

8. Thirty-one episodes of bacterial sepsis.
 9. Opportunistic Infections (20 TB, 15 viral, 13 legionnaires, 4 aspergillosis, 3 pneumocytis)
- F. Tuberculosis
1. Tuberculosis: in first 12 months, 13 cases noted (8 RA, 5AS)-on infliximab 7, Humira 6, etanercept 1.
 2. This data suggests that despite guidelines on anti-TNF medications, TB is still a major problem. Guidelines should be revisited and perhaps not disregarding the 5 mm positive PPD.
- G. Lymphoma
1. Thirteen patients developed lymphoma during the year (4 Hodgkins, 1 diffuse B cell, 1 Mast B cell lymphoma with Sjogrens (10 RA, 2 AS, 1 Sjogrens)
- H. Conclusions
1. Surveys must be national
 2. Participation must be made mandatory and keep pushing them
 3. Good example btw cooperation of gov and medicine and pharmo
 4. Led to change in length of treatment for prophylaxis to make it longer and reduction of PPD positivity back to 5 mm