

Report from the PReS Meeting in Versailles, France Sept 2005 Clinical Presentations

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I Clinical study: IVIG therapy for pediatric polyarteritis nodosa-P Quartier (Paris)

- A. Working Group is presently devising diagnostic criteria
- B. These will include some combination of fever, weight loss, skin lesion (often transient), arthralgias, arthritis, myalgia, abdominal pain, hypertension
- C. In this study 27 patients were evaluated (16 girls, 11 boys)
- D. Biological markers utilized included: Signs of marked systemic inflammation with increased WBC and ESR, no eosinophilia, no elevated ANCA titers.
- E. Biopsy best means of diagnosis often skin with typical fibrinoid changes in the blood vessel wall.
- F. Treatment
 1. An NSAID was begun at diagnosis in 20/27 patients.
 2. In 7 patients corticosteroids -effective in 6
 3. IVIG
 - a. Six female, 4 male patients
 - b. Each had more severe skin and systemic involvement that did not respond to previous treatment (9 NSAID's, 1 cyclophosphamide)
 - c. Protocol: monthly IVIG for six months.
 - d. An excellent clinical response was seen in 9/10.
 - 1) Five did not require steroids again.
 - 2) Nine did well compared to previous treatment regimen
 4. Conclusions
 - a. Consider IVIG early with NSAID's for milder forms
 - b. Steroid sparing effect is useful in relapsing or more severe PAN disease.
 - c. PAN in childhood is a rare disease so we may need an international trial.

II Clinical Study: Rituximab in SLE-Willem (Le Kremlin-Bicetre, France)

- A. Twenty-four adult patients have been reported that have been treated successfully for autoimmune hemolytic anemia with rituximab; One child with SLE with ITP has been similarly treated
- B. This was a multicenter (12 hospitals in France) retrospective study of rituximab use in juvenile SLE that included 11 patients with severe SLE diagnosed before age 16 years by the ACR SLE criteria.
 1. Eight with nephritis (6 with WHO Class IV previously treated with cyclophosphamide)
 2. One each with autoimmune anemia, autoimmune thrombocytopenia, or antiprothrombin antibody
- C. The mean age at onset of rituximab treatment was 13.9 years old.
- D. The patients received from 2-7 infusions at standard dose of 375-450 mg/m². Premedications with an antihistamine and acetaminophen were given in 9/12. Two patients received cyclophosphamide as well. Two patients were taking cyclosporine or methotrexate.
- E. Results: Remission was achieved in 5 patients with lupus nephritis and two with cytopenia (mean follow-up 13 months). Anti-DNA antibodies decreased in 6/11 and anticardiolipin antibodies in 3/6 patients. C3 and C4 levels normalized in 5/8. Depletion of peripheral B cells was observed in 7/8 patients tested with poor responders having only a transient lowering of the peripheral B cells.. Two patients definitely failed rituximab therapy and in two patients it was inconclusive. Three patients developed adverse events (neutropenia, infection-sepsis).

- F. Conclusion: Rituximab was effective in 7/11 children with severe SLE in achieving short-term improvement with some side effects.

III CLINICAL STUDIES

- A. Adverse events in JIA taking etanercept and methotrexate.
1. British Collaborative Group-12 British centers
 2. Post-marketing experience over 4 months in 2005 in patients with JIA.
 3. 122 JIA patients on Enbrel, 30 patients on methotrexate.
 4. Enbrel patients' mean age was 11 years, methotrexate group 8 years.
 5. Enbrel JIA patients had more severe disease.
 6. 62 patients suffered at least one adverse event.
 7. 145 patient years of exposure.
 8. The patients on etanercept experienced 72 total adverse events for Enbrel while patients on methotrexate had 70.
 9. Gastrointestinal problems were greater in methotrexate patients while both groups had infections to a relatively equal extent.
 10. Enbrel patients had 8 serious adverse events including 4 disease flares, hypertension, sepsis, and skin rash.
 11. Methotrexate-nausea, abnormal liver function tests, menstrual problems, panic attacks, mood changes, increased anxieties.
- B. Juvenile dermatomyositis and muscle disease.-Alexii Grom
1. What is reason for vasculopathy in JDM? CXC chemokines may provide explanation of persistent angiostatic problems, e.g., IP-10.
 2. Study of 7 pretreatment JDM muscle biopsies compared to 9 muscle biopsies done for neurological disease and 7 JIA biopsies
 3. Results:
 - a. All dermatomyositis specimens had positive results, e.g., Ip-10 was found in areas of muscle with perifascular atrophy;
 - b. MIG mRNA expressed in large amounts in JDM compared to normal and JIA muscle samples.
 - c. These findings correlated well with the loss of capillary bed and myofibrosis findings typical of vasculopathy.
 - d. IP-10 was found in blood vessel walls and CXCR3 expressed in endothelium.by immunohistochemistry.
 - e. ELR-CXC chemokines is a feature of JDM that correlates with vasculopathy. The vaculopathy may be correlated with IFN-alpha induction.
This brings up the question: Is JDM a disease of blood vessels more than a muscle disease?
- C. Juvenile systemic sclerosis-Francisco Zulian
- 1 .At the first juvenile scleroderma consensus conference, the preliminary juvenile scleroderma classification criteria were chosen-One major criterion and one minor criterion or 2 major criteria.
 - 2 The challenges were how to detail better the clinical and immunological information and also how to describe organ involvement.
 3. The conference met again in June 2004. The group had developed a large data bank of patient data.
 4. A pre-conference survey was done assessing organ involvement and possible criteria, major and minor with rankings.
 5. The survey also considered prevalence of JSS signs and symptoms at diagnosis e.g., Raynaud's at 76%.
 6. Top three criteria selected were Raynaud's, sclerosis/induration, sclerodactyly; 18 minor criteria identified.

7. Tested criteria with the data of 181 patients in the group's data bank with awareness of confounding factors such as overlap syndrome.
8. Evaluated 160: 73/160 all agreed had scleroderma; 57 all agreed did not have scleroderma; 21 no consensus as to whether scleroderma was the right diagnosis or not.
9. Next all criteria tested as well from many other sources with statistical analysis – Then ranked top 10 prelim criteria-using this approach
10. Thus far the diagnosis requires the presence of sclerosis/ induration plus 2/19 minor criteria.

IV Example of “Meet the Professor”- Uveitis- Bodaghi (Paris)

A. Uveitis characteristics in JIA with systemic, polyarticular, and oligoarticular onset.

1. Bilateral in 75%
2. Onset usually asymptomatic
3. Non-granulomatous
4. Spill over vitritis
5. Moderate level of corneal deposits
6. Long-term visual prognosis may be poor

B. Uveitis in spondyloarthropathy in children

1. Very different disease in juvenile spondyloarthropathy
2. Often unilateral
3. Acute onset with symptoms frequently present
4. Usually responsive to steroids drops

C. Complications of chronic uveitis band

1. Band keratopathy
2. Synechiae
3. Glaucoma
4. Cataract,
5. Posterior segment disease

D. Laser Flare Photometry

Laser Flare Photometry (LFP) can quantitate the degree of flare much more than 1+ to 4+ flare scoring used in conventional slit lamp exams. This technique is non-invasive, but does require some cooperation from the child. It is a major help in monitoring uveitis. It is used extensively in Europe but not use in North America.

Here is an illustrative study utilizing LFP in uveitis of JIA.

The study attempted to distinguish the more severe, poor prognosis uveitis patients from the milder course, better prognosis JIA uveitis patients.

Group A-severe Group B-milder; mean follow-up 3 years

Results:

Group A-10 patients with a mean flare ranging from 237 at onset of treatment to 125 after aggressive therapy.

Group B-14 pts with a mean flare 72.8 initially to 26.5 after aggressive therapy.

Five patients in Group A developed glaucoma compared to 3 patients in group B.

Five patients in Group A required cataract removal surgery and none in Group B.

This study appeared to demonstrate that LFP could help separate the children with a more difficult prognosis with their uveitis from those with a better prognosis. LFP appears to be particularly useful in guiding therapy when the uveitis is at a low level of inflammation.

This assessment of low level of uveitis inflammation can be very hard with the slit lamp

E. Treatment:

1. Steroid drops/injections
2. NSAID
3. Mydriatics
4. Prednisone (more in Europe than North America, especially in

France)

5. Cyclosporine A is not used much in France due to retinitis side effect.
6. Methotrexate
7. Azathioprine
8. Etanercept
9. Infliximab
10. Humira

Comments: Dr. Bodaghi and his group have not used mycophenolate yet but it may turn out to be useful. In the US, ophthalmologists often bypass oral corticosteroids to utilize methotrexate and do it earlier and earlier. There appears to be a trend in the same direction in some parts of Europe, e.g., in Finland. The anti-TNF alpha medication etanercept has been studied recently for uveitis and no benefit was shown by slit lamp exam. But there may be a benefit in introcular lens implantation (IOL) Requires aggressive immunosuppression steroids and mtx-no eye glasses allowable, usually < 5 years Vitreous inflammation=pars planis-if no uveitis, watch- if uveitis very active, must go to immunosuppressive and treatment is often very long for macular edema Optic Coherence Tomography needed for posterior uveitis complications that produces macular edema.

F. High risk JIA uveitis patients:

1. Boys more than girls
2. Short duration from diagnosis of JIA to uveitis onset
3. No change in the prognosis of this group in the last decade.
4. Suggest q 6 month visits for high risk kids x 2 years, then q year

G. Notes about other diseases:

1. Behcet's syndrome eye disease requires aggressive approach with immunosuppressives; papilledema or papillitis vitriitis not uncommon.
2. Tips:
 - a. If note granulomatous keratin infiltrates-check retina as you may see new and old lesions secondary to toxoplasmosis.
 - b. Papillitis-cat scratch disease
 - c. Peripheral retinal necrosis, red infiltrates, ant uveitis seen, think of herpes

H. Conclusions:

1. Multidisciplinary approach needed.
2. Aggressive surveillance and early treatment
3. Don't under-treat and don't allow smoldering inflammation.
4. LFM seems to be a helpful tool for the monitoring anterior uveitis
5. 75% reduction after initial anti-inflammatory eye drops is a good prognostic sign.
6. Surgery may be needed for selective problems.

Uveitis case presentation #1:

4 cases of optic neuritis with treatment with etanercept.

3 females, 1 male all at a dose 25 mg subcutaneously 2x/week

a. Case 1-12 yr old

oligo JIA at age 3 years developing to extended oligoarticular.

Treatment included intravenous methotrexate and intraarticular steroids. Etanercept added and the drug helped the joint problems. But at age 8 uveitis developed; the uveitis was treated conventionally but a cataract was noted. Optic neuritis started 2 ½ months after the cataract was noted. The optic neuritis was confirmed by ultrasonography and the etanercept was stopped.

b. Case 2

Etanercept started for arthritis and 8 months later the child developed optic neuritis.

- c. Case 3
20 yr old with JIA due to psoriasis; etanercept helped with severe arthritis but 1 ½ years later she developed optic neuritis.
- d. Case 4
18 year old with spondyloarthropathy whose arthritis was not nearly as bad as his uveitis, especially in the right eye. At first cyclosporine A was begun and he developed hearing loss and cyclosporine was stopped. Then he was switched to etanercept His eyes then went into remission for first time. But 9 months later he developed optic neuritis. Due to the benefits, the patient chose to continue the etanercept and his eyes stabilized.

Uveitis case presentation #2-preliminary results

Evaluation of etanercept versus infliximab for uveitis secondary to JIA.

108 total patients with uveitis evaluated.

- a. 46/108 with severe uveitis treated had been treated with mtx-all but 4 had been on methotrexate before uveitis was diagnosed.
- b. 20 on infliximab-all 20 had been on infliximab prior to uveitis.
- c. 24 on etanercept-20 begun on the drug prior to uveitis noted.
- d. Results

Etanercept-3 better by their outcome measures

Infliximab-9 better

Etanercept flare-ups:1.35 per year

Infliximab flare-ups were 0.71 per year (p=0.025)

V Clinical Heuristics and Diagnostic Problem Solving: A talk for rheumatologists in training. Balu Athreya (Wilmington, Delaware, USA)

A. Basics

The definition of heuristics: Relating to or constituting an educational method in which learning takes place through discoveries made by the students from investigations of the students. This can also mean making your mind work in a way that is transferable to a machine such as a computer with its organizational logic and problem-solving techniques. You ask what is in a patient's case that I am able to understand and what is in the case that I do not understand it and how does it add up to knowing what to do.

These problem-solving skills can be learned. You need to develop more creative, constructive techniques. They should not be reflexive, a knee-jerk response, but rather reflective, choosing a diagnostic plan or treatment regimen after some reflection. So heuristics involves learning from each experience and learning how mind works in solving problems.

This is important in this age of mega-workups and of information overload. It involves learning from contemplative learning. You need to be aware of mental process, need to think, and need time to think. In busy schedules these days having time to think can be a challenge. Don't expect the kids to read the book and fit neatly into diagnostic categories. As Sidney Gellis of Boston once said: "If you are someone who likes every piece to fall in place, you should be in carpentry".

How does your mind work?

So as a physician you start with your patient—You ask a question-You analyze your own mental process based on the questions you ask and see how you problem-solve.

You should start with a system of history, physical exam, laboratory, and assessment in detail. Yet it is OK to jump around some and to hound-dog and go out on a trail, but come back when the scent disappears. Words can get in the way-flexion contractures versus flexion deformities. Is it arthritis versus an arthropathy? Is there inflammation?

Don't swallow the diagnosis of someone else? Look at it afresh. Why it is necessary for us to rethink medical problems and not accept others assessments? One reason is that we are trained to compete-We also often have limited data; children's diseases often evolve gradually and the information you have now may be different than the data another physician had to evaluate.

B. Some history of the heuristic approach in medicine:

1. Voltaire-"Those who make you believe absurdities can make you commit atrocities"
2. Voltaire: the **Method of Zidig** with retrospective prophesy-reconstructing the broken glass.
3. Giovelli Morelli-systematic attention to detail leading to logical conclusions.
4. Thomas Henry Huxley-get to the point, don't let the patient free associate and go on and on.
5. A manuscript: **The Art of Diagnosis**: David Eddy and Charles Clanton NEJM 1982
6. Aggregate element findings
You start with any single piece of information and then build up to an aggregate of information by combining 3 or 4 pieces of information. This is crucial as your mind tends to aggregate information, using high abstraction to achieve an aggregate with fewer information pieces to remember. Remember that the human mind can only hold up to 7 facts at a time and your mind cuts it off there.
7. Arrange findings in a creative way.
 - a. Selection of a pivot-move from a list of findings to a list of causes-choose one pivot, a single item or an aggregate with a decision to ignore other findings. Generate a list of causes that does not try to explain everything.
 - b. Move from textbook to patients to design the list of causes.
 - c. Prune the list and compare one by one the patient's findings and symptoms of disease-look out the pattern in the list-If you are fortunate you will end up with only one!!
 - d. Seek comparisons and not equalities.
8. Then select the diagnosis. To do so, take diseases 2 or 3 at a time-then also bring in the lab or other data and make your assessment and choose one disease. Then validate this conclusion-Can this disease explain all the findings?-if not, realign the aggregate, choose a different pivot and start all over.

C. Major areas of deficiency/errors

1. Very early hypothesis generation is problematic-making an early decision and staying with it, regardless of later signs, symptoms, lab, and course.
2. Patient already has a diagnosis and you accept it on face value.
So when you hear the patient's symptoms and signs and the previous diagnosis, then define: What is the patient's problem? Exclude-What is the diagnosis now-Confirm-How can you know for sure?

D. Concept of a critical question:

There is always one critical question and you must look for it. That critical question can make all the difference.

It could be that the fit is excellent or not perfect. It could be that the patient's features that don't fit the best diagnosis may not be described yet but may be in the future. Accept the diagnosis for now but keep your mind open. So for now go with the diagnosis but be alert for future changes and possible other diagnoses.