Cardiac Neonatal Lupus: Long-Term Data Show More Problems with Aging

Written by Wayne Kuznar

According to long-term follow-up of patients from the Research Registry for Neonatal Lupus (RRNL), patients with cardiac manifestations of neonatal lupus (NL) are more likely to develop an enlarged heart and the need for pacemaker replacement as they age. The findings emphasize the need for continued long-term cardiac evaluation of patients with cardiac-NL. They were presented by Amit Saxena, MD, New York University School of Medicine, New York, New York, USA, the lead investigator of the analysis [Saxena A et al. ACR 2012 Poster 290].

NL is a model of passively acquired autoimmunity. It occurs when anti-SSA/Ro and/or SSB/La antibodies cross the placenta and make their way into the fetal circulation. The greatest morbidity and mortality occurs from irreversible damage to the heart, for example due to congenital heart block or cardiomyopathy, said Dr. Saxena. Long-term cardiac and rheumatologic outcomes as well as those related to neurodevelopment have not been formally assessed.

Family members of 75 children from the RRNL with cardiac-NL completed questionnaires, as did 35 families of children with cutaneous NL and 74 unaffected siblings. Twenty-four percent of the children were 0 to 5 years old at latest follow-up, 27% were 5 to 10 years old, 11% were 10 to 15 years old, 21% were 15 to 20 years old, and 17% were >20 years old. Eighty-five percent of the children had third-degree heart block.

Questionnaire responses revealed that 74% of the children had a pacemaker implanted and 65% needed a replacement pacemaker. Forty-one percent of family members had ever been told that their child had a dilated heart and 20% had ever been told that their child had congestive heart failure. One child had undergone heart transplant.

When cardiac outcomes were examined by age group, older age was associated with a reported history of an enlarged heart (p=0.016), a greater need for pacing (p=0.001), and a greater likelihood of having a pacemaker replaced (p=0.003; Table 1). Of the 37 children with cardiac-NL who were aged >10 years, 19% required cardiac medications (ie, digoxin, angiotensin-converting enzyme inhibitors, or β-blockers) compared with 5% of those aged <10 years (p=0.086).

Table 1. Long-Term Data May Show More Problems with Aging.

Age (years)	n	Total CHF	TDH*	Paced*	PPM Replaced*	Cardiac Meds†
0–5	18	4 (22%)	5 (28%)	10/17 (59%)	0 (0%)	1 (6%)
5–10	20	2 (10%)	4 (20%)	11/17 (65%)	8/11 (73%)	1/18 (6%)
10–15	8	3 (38%)	6 (75%)	6 (75%)	5/6 (83%)	2/7 (29%)
15–20	16	3 (19%)	9 (56%)	13 (81%)	10/12 (83%)	2 (13%)
>20	13	3 (23%)	7 (54%)	13 (100%)	9/10 (90%)	3/11 (27%)

*Median age higher in those reporting enlarged heart (p=0.016), needing a PPM (p=0.001), and PPM replacement (p=0.003). †Of 37 children >10 years, 19% required cardiac medicine (digoxin, ACE inhibitor, or β blocker) versus 5% of 36 children <10 years (p=0.086). CHF=congestive heart failure; PPM=permanent pacemaker; TDH=total dilated heart.

Children who had dilated cardiomyopathy or valvular disease on their fetal echocardiogram had significantly more pacemakers replaced as they got older compared with those without these features on their fetal echocardiogram (p<0.05).

Twelve percent of children with cardiac-NL had delayed motor milestones compared with only 3% of unaffected siblings (p=0.027), but there was no difference in intellectual delay between these groups (19% vs 15%, respectively).

Fluorinated Steroids in Cardiac Neonatal Lupus Do Not Impact Survival

Written by Wayne Kuznar

Exposure to fluorinated steroids does not seem to have an impact on fetal survival in cardiac neonatal lupus (NL), with the possible exception of fetuses with hydrops. Available data are discordant regarding the efficacy of fluorinated steroids in the prevention of fetal mortality in cardiac-NL. In a study in which patients with fetal complete atrioventricular (AV) block were treated with dexamethasone, mortality at 1 year was 10%, compared with a mortality rate of 54% in historical controls, although the historical controls used clearly had much higher rates of poor prognostic factors [Jaeggi ET et al. *Circulation* 2004]. In contrast, no significant effect of treatment with fluorinated steroids on mortality was observed in a retrospective multicenter study of 175 fetuses diagnosed with second- or third-degree AV block [Eliasson H et al. *Circulation* 2011].

Similarly, the available data on the prevention of cardiac-NL with the use of fluorinated steroids are limited, with one study that showed effective prevention of congenital

heart block with maternal fluorinated or nonfluorinated steroids [Shinohara K et al. *Obstet Gynecol* 1999] and a review that failed to find utility of prophylactic treatment of congenital heart block [Costedoat-Chalumeau N et al. *Rev Med Interne* 2003].

Given the uncertainty over the benefit of fluorinated steroids and the maternal and fetal risks associated with these agents, the use of fluorinated steroids on the survival of fetuses with cardiac-NL and the protection from recurrent disease was investigated by Peter M. Izmirly, MD, New York University School of Medicine, New York, New York, USA. Data sources for the investigation were the Research Registry for Neonatal Lupus (RRNL) and an international historical control of 257 pregnancies following the birth of a child with cardiac-NL (which comprised cases in the US-based RRNL, France, and the United Kingdom). The outcomes assessed were fetal survival at 6 months and the recurrence rate of cardiac-NL.

Of the 276 cardiac-NL pregnancies in families enrolled in the RRNL, 150 were treated with fluorinated steroids and 126 were not. Gestational age at detection was 22.1 weeks in those treated with fluorinated steroids versus 24.4 weeks in those not treated ($p<0.0001$). The average dose of dexamethasone in those treated was 4.1 mg for an average duration of 10.9 weeks. Of fetuses with isolated third-degree block at presentation, there were 2 deaths at 6 months in the 78 treated with fluorinated steroids and no deaths in the 74 not treated with fluorinated steroids.

Any benefit to fluorinated steroids appeared to be restricted to those cases associated with hydrops: 13 of 27 (48.1%) with hydrops who were treated with fluorinated steroids were alive at 6 months compared with 1 of 10 (10.0%) not treated with fluorinated steroids ($p=0.059$).

There was no difference in the case fatality rate among treated and nontreated patients with at least 2 poor prognostic risk factors (heart rate ≤50 beats/minute, dilated cardiomyopathy, or endocardial fibroelastosis; Table 1).

Table 1. Effect of Fluorinated Steroids on Case Fatality Rate in Cardiac NL with Associated Poor Prognostic Factors.

Associated Manifestation	Fluorinated Steroids (Case Fatality Rate)	No Fluorinated Steroids (Case Fatality Rate)
DCM	1/4	1/5
EFE	1/11	0/1
≥2 Poor prognostic factors (HR ≤50 bpm, DCM, EFE)	1/6	2/6

bpm=beats per minute; DCM=dilated cardiomyopathy; EFE=endocardial fibroelastosis.

Among the international historical controls of pregnancies following the birth of a child with cardiac-NL, the overall recurrence rate was 19.1%, with no significant difference in the recurrence rate between those treated and not treated with fluorinated steroids (14.3% vs 19.3%; $p=0.58$; Table 2).

Table 2. Exposure to Fluorinated Steroids Does Not Reduce the Recurrence Rate of Cardiac NL.

	Fluorinated Steroids	No Fluorinated Steroids
Unaffected	12	196
Cardiac Neonatal Lupus	2 2/14 (14.3%)	47 47/243 (19.3%)

p=0.58.

Tocilizumab Significantly Reduces Flares in Polyarticular Juvenile Idiopathic Arthritis

Written by Wayne Kuznar

Treatment with tocilizumab, a humanized monoclonal antibody that interrupts interleukin-6-mediated signaling, results in meaningful improvement of polyarticular-course juvenile idiopathic arthritis (pcJIA) following methotrexate failure, with treatment responses maintained to at least 40 weeks, said Hermine I. Brunner, MD, MSc, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA.

The finding comes from A Study of Tocilizumab in Patients with Active Polyarticular-Course Juvenile Idiopathic Arthritis [CHERISH; NCT00988221], a 3-part trial in which patients aged 2 to 17 years with pcJIA who had at least 5 joints with active arthritis were randomized to treatment with tocilizumab 8 mg/kg or 10 mg/kg, depending on body weight, or placebo after an open-label run-in. To be eligible, patients had to have an inadequate response to or an inability to tolerate methotrexate and had to be on a maximum stable dose of oral corticosteroids (10 mg/day or 0.2 mg/kg/day—whichever was lower).

In Part 1 of the study, 188 patients received intravenous infusion of tocilizumab (8 mg/kg for patients ≥30 kg, 8 mg/kg or 10 mg/kg for patients <30 kg) in an open-label fashion for 16 weeks. In Part 2, 166 patients who had an adequate response in Part 1 were randomized to receive either tocilizumab at the same dosage as in Part 1 or placebo, every 4 weeks for up to 24 weeks. In Part 3, patients will receive tocilizumab at the same dosage as in Part 1, every 4 weeks for up to another 64 weeks. Standard-of-care therapy was continued throughout the study. Data from Parts 1 and 2 were presented by Dr. Brunner.