Clinical and Experimental Rheumatology 2001; 19: 487-489.

Modern treatment of childhood SLE

T.J.A. Lehman

Thomas J. A. Lehman, MD, Chief, Division of Pediatric Rheumatology, Hospital for Special Surgery, and Professor of Clinical Pediatrics, Sanford Weill Medical Center of Cornell University, Hospital for Special Surgery, 535 East 70 Street, New York, NY 10021, USA. E-mail goldscout@aol.com

Received on May 10, 2001; accepted on June 21, 2001.

© *Copyright CLINICAL AND EXPERIMENTAL RHEUMATOLOGY 2001.*

When considering the special needs of children with SLE, most physicians are aware of the problems associated with parental anxiety and adolescent "acting out." However, few recognize the far more dramatic needs associated with true long-term survival. For a fifteen-year-old with new onset SLE, five-year survival is only to age twenty, and ten year survival is only to age twenty-five. The goal for a fifteen-year-old with SLE is fifty or even sixty year survival !! Long term moderate or high dose corticosteroid therapy (more than 0.2 mg/kg/day) is associated with an unacceptable incidence of osteoporosis, avascular necrosis of bone, premature arteriosclerosis, and psychological damage secondary to altered appearance (1-3). We cannot be content controlling SLE with corticosteroids alone. Nor can we be content with many years of treatment with cytotoxic or other immunosuppressive drugs and their associated toxicities (4-6). Instead, we must be guided by our colleagues in oncology. Our goal is not a lifetime of disease suppression. Our goal must be to cure the disease !!

Can we cure SLE? Is drug-free remission possible? The first step is to recognize that SLE is not a homogeneous disease. Some children have mild SLE with little or no internal organ involvement and can be managed with non-steroidal anti-inflammatory drugs and/or minimal amounts of corticosteroids. Aggressive intervention is not appropriate. Others have severe disease with immediate life-threatening complications such as pulmonary hemorrhage, diffuse proliferative glomerulonephritis, or central nervous system involvement, which mandate aggressive intervention. Many more children have persistent SLE controlled by chronically rising and falling dosages of corticosteroids. This group must be treated more aggressively to prevent excessive morbidity and mortality.

Over the past twenty years the outlook for children and adults with SLE has improved dramatically (7-9). Much of the improvement may be ascribed to improved antibiotic regimens and improved intensive care unit support for critically ill children. However, many children continue to do poorly between ten and twenty years following diagnosis. Both complications of therapy and patient non-compliance are significant causes of morbidity and mortality in this group (10). When questioned, many of these young adults state that they are simply "tired of taking the medicine" and "tired of having a disease." Physicians caring for children and adolescents with SLE must develop regimens which avoid these frustrations.

Many children with diffuse proliferative glomerulonephritis have been treated with systematic courses of intravenous cyclophosphamide with great success (11, 12). Some remain off all corticosteroids four years following their last dose of cyclophosphamide in apparent drug free remission. Most are in sustained remission, but continue on 7.5 -10 mg of prednisone daily (≤ 0.2 mg/kg/day) because of historical concern that they might flare if the dosage is reduced. In my series, the majority of the children have normal serum complement levels and in some cases negative ANAs.

Many physicians are concerned about the potential long term toxicities associated with the systematic use of intravenous cyclophosphamide. Others have argued that they can obtain disease control with the daily use of azathioprine or mycophenolate mofetil (13). There is reported experience with these regimens in adults, but no pediatric series (14). It is clear that there may be a variety of successful regimens. However, the intravenous cyclophosphamide experience is the only published series describing successful long term treatment of childhood SLE. Attempts to utilize a shorter course of cyclophosphamide followed by another agent lack validation.

Can we attain a similar degree of disease remission for children with non-renal SLE? Should we accept the risks of intravenous cyclophosphamide therapy in our efforts to attain this goal? Over the past twelve years at the Hospital for Special Surgery we have treated children with persistent non-renal SLE with a one year course of intravenous cyclophosphamide (7 monthly

doses followed by two additional doses at three month intervals). The indications for intravenous cyclophosphamide therapy in this setting are persistent hypocomplementemia which cannot be corrected with less than 0.33 mg/kg/day of prednisone or its equivalent, persistent hypertension (diastolic >90 mm Hg) for more than six months despite routine anti-hypertensive medications, persistent anemia (Hb < 10 gms/dl) for more than six months, recurrent or corticosteroid resistant central nervous system manifestations, or pulmonary hemorrhage (15).

Our experience suggests that intravenous cyclophosphamide can be safely administered over a one to three year horizon (9 - 17 gms/M^2 of cyclophosphamide) with minimal short or long term toxicity. All children are hospitalized and given the intravenous cyclophosphamide only after a twelve hour period of hospital observation to assure that they are afebrile and well hydrated (7). All receive intravenous MESNA following the infusion of cyclophosphamide, and all receive twenty-four hours of in-hospital intravenous hydration following the cyclophosphamide infusion. Utilizing this regimen we have had no significant toxicity associated with the normal course of intravenous cyclophosphamide therapy. Two patients who received six years of intravenous cyclophosphamide (> 30 gms/M^2) experienced long term toxicity (one developed "fixed" amenorrhea and one developed a renal papillary cell carcinoma). We now utilize an alternative regimen for children who do not make satisfactory progress on cyclophosphamide (see the salvage protocol described below).

A variety of minor problems have been experienced while treating children with intravenous cyclophosphamide. In the initial stages of disease control some children have continuing leukopenia at the time they are scheduled for their next monthly dosage of intravenous cyclophosphamide. This can be corrected by treating them with intravenous methylprednisolone (30 mg/kg up to 1 gram given intravenously over one hour). Surprisingly most patients respond to the first infusion of intravenous methylprednisolone with a decline in their total white blood cell count. We repeat the methylprednisolone 24 hours later and in most cases the white blood cell count then rises in six to twelve hours to an acceptable level. This treatment provides additional therapy for the child's continuing active SLE while demonstrating that the child has adequate marrow reserves to mount a stress response despite the initial leukopenia. No child so treated has developed sepsis following the subsequent infusion of intravenous cyclophosphamide. In general this therapy may be necessary on three or four occasions, but in our experience it has never been necessary after the first six months of therapy. Only one child has failed to respond to this regimen with a satisfactory increase in the total white count. This child was discharged on an increased daily dose of corticosteroids and returned with a satisfactory white blood cell count two weeks later and continued therapy without difficulty.

Although the routine use of intravenous cyclophosphamide has been very successful, not all children respond completely. Several patterns of poor response are apparent. A few children have failed to improve during the first six months of intravenous cyclophosphamide. Some children initially respond well, but fail to maintain their response when the dosage interval is extended to three months. Others responded well during the three years of intravenous cyclophosphamide therapy, but developed recurrent disease thereafter. For children who develop persistent disease while being treated for severe non-renal SLE we will extend the course of therapy to the full three years (this has only been necessary on rare occasions).

Most children brought to our attention by other centers because they failed to improve during the first six months of therapy were children who developed leukopenia and the subsequent dosages of intravenous cyclophosphamide were held despite continuing active disease. We have been uniformly successful in treating this problem with intravenous methylprednisolone as noted. In our hands only one child has worsened during the initial six months of intravenous cyclophosphamide therapy. This child was entered into the "salvage protocol" discussed below. Children who develop recurrent disease with the transition from monthly intravenous cyclophosphamide to every three month cyclophosphamide are treated with three additional doses of intravenous cyclophosphamide given at monthly intervals. This has been effective for the majority. Those with continuing active disease despite this modification also should be entered into the salvage protocol.

In the course of treating 41 children with DPGN with intravenous cyclophosphamide, four have developed recurrent disease after completing the initial three year course. These children have been entered into a "salvage protocol." In this protocol the children are treated with a regimen of intensive chemotherapy with the goal of attaining long term disease remission without the excessive toxicity associated with prolonged cyclophosphamide therapy. After complete reevaluation the children were all begun on daily folic acid (1 mg/day). Each then received nine months of therapy with intravenous cyclophosphamide at the previously tolerated dosage of 750 - 1000 mg/M^2/month. With each dose of cyclophosphamide, intravenous methotrexate was administered in a gradually escalating dose from 50 - 300 mg/M^2/month, as tolerated. The methotrexate was administered over four hours beginning four hours after completion of the infusion of intravenous cyclophosphamide. Good control of the SLE activity was attained for all four children (16). However, leukopenia,thrombocytopenia, nausea, and malaise were more severe for these children than for those receiving intravenous cyclophosphamide alone. Over an average of 18 months of follow-up, none has had a further SLE flare.

Several alternative regimens have been proposed for the treatment of severe SLE. Successful use of hematopoetic stem cell transplantation combined with chemotherapy has been utilized in adults and in some adolescents (17-19).

However, many patients have experienced recurrent disease following this regimen. In addition one child who received an autologous stem cell transplant for SLE died of infection before bone marrow recovery. Short term, very high dose intravenous cyclophosphamide therapy (4 gms/m^2) has also been proposed and is being tested in adults, but not yet validated. Whether these therapies will prove more satisfactory over the long term is unclear.

The routine use of intravenous cyclophosphamide therapy for both diffuse proliferative glomerulonephritis and for children with non-renal lupus which was not responsive to a low dose of corticosteroids has allowed us to avoid most of the significant corticosteroid associated toxicity in the children we treat. Often these children tell us that between physician visits they are able to "forget" that they have lupus. Some children may have recurrent disease over time, but the majority are without significant disease or treatment related morbidity. Over the next decade we must intensify our efforts to develop further regimens with the goal of fifty or sixty year survival without either disease or treatment related morbidity and mortality. Systematically administered intravenous cyclophosphamide is a solid step in that direction. More intensive protocols combining multiple agents may be necessary for those who do not respond.

References

1. HOLLISTER JR: Medical treatment of adolescents with rheumatic disease. *Adolescent Medicine* 1998; 9: 163-70.
2. ZONANA-NACACH A, BARR SG, MAGDER LS, PETRI M: Damage in systemic lupus erythematosus and its association with corticosteroids. *Arthritis Rheum* 2000; 43: 1801-8.
3. GINZLER EM, ARANOW C: Prevention and treatment of adverse effects of corticosteroids in systemic lupus erythematosus. *Baillières Clin Rheumatol* 1998; 12: 495-510.
4. D'CRUZ D, CUADRADO MJ, MUJIC F *et al.*: Immunosuppressive therapy in lupus nephritis. *Clin Exp Rheumatol* 1997; 15: 275-82.
5. ARNOLD JA, RANSON SA, ABDALLA SH: Azathioprine-associated acute myeloid leukaemia with trilineage dysplasia and complex karyotype:A case report and review of the literature. *Clin Lab Haematol* 1999; 21: 289-92.
6. TANIS AA: Azathioprine in inflammatory bowel disease, a safe alternative? *Mediators of Inflammation* 1998; 7: 141-4.
7. LEHMAN TJ: Long-term outcome of systemic lupus erythematosus in childhood. What is the prognosis? *Rheum Dis Clin North Am* 1991; 17: 921-30.
8. UROWITZ MB, GLADMAN DD, ABU-SHAKRA M, FAREWELL VT: Mortality studies in systemic lupus erythematosus. Results from a single center. III. Improved survival over 24 years. *J Rheumatol* 1997; 24: 1061-5.
9. GLOOR JM: Lupus nephritis in children. *Lupus* 1998; 7: 639-43.
10. PLATT JL, BURKE BA, FISH AJ, KIM Y, MICHAEL AF: Systemic lupus erythematosus in the first two decades of life. *Am J Kidney Dis* 1982 Jul. 2 (1 Suppl 1):-22.
11. LEHMAN TJ, ONEL K: Intermittent intravenous cyclophosphamide arrests progression of the renal chronicity index in childhood systemic lupus erythematosus. *J Pediatr* 2000; 136: 243-7.
12. LEHMAN TJ, SHERRY DD, WAGNER-WEINER L *et al.*: Intermittent intravenous cyclophosphamide therapy for lupus nephritis. *J Pediatr* 1989; 114: 1055-60.
13. SILVERMAN ED, LANG B: An overview of the treatment of childhood SLE. *Scand J Rheumatol* 1997; 26: 241-6.
14. DOOLEY MA, FALK RJ: Immunosuppressive therapy of lupus. *Lupus* 1998; 7: 630-4.
15. MCCURDY DK, LEHMAN TJ, BERNSTEIN B *et al.*: Lupus nephritis: Prognostic factors in children [see comments]. *Pediatrics* 1992; 89: 240-6.
16. EDELHEIT BS, ARKACHAISRI T, ONEL KB, LEHMAN TJ: Combined chemotherapy with intravenous cyclophosphamide and intravenous methotrexate for systemic lupus erythematosus. *Arthritis Rheum* 2000; 43 (Suppl.): S321.
17. TRAYNOR A, BURT RK: Haematopoietic stem cell transplantation for active systemic lupus erythematosus. *Rheumatology (Oxford)* 1999; 38: 767-72.
18. BURT RK, TRAYNOR A: Hematopoietic stem cell therapy of autoimmune diseases. *Curr Opin Hematol* 1998; 5: 472-7.
19. WULFFRAAT N, SANDERS EAM, KAMPHUIS SSM *et al.*: Prolonged remission without treatment after autologous stem cell transplantation for refractory childhood systemic lupus erythematosus. *Arthritis Rheum* 2001; 44: 728-31.