

Immunomodulatory Therapy for Children With Steroid-Resistant or Steroid-Dependent Uveitis

C. Stephen Foster, M.D.

The purpose of this presentation is to provide to you the results of an assignment given to me by Dr. Holland, namely, to review the matter of immunomodulatory therapy in children, in particular in children with uveitis. In an effort to discharge this responsibility given to me, I reviewed the literature relevant to pediatric immunomodulatory therapy for non-malignant, non-ocular disease in an effort to determine, to the extent possible, information regarding the safety of such therapy for children with non-malignant disease. Additionally, I have reviewed the literature on immunomodulatory therapy in children with ocular inflammatory disease. The central question I have tried to address is that of, "What is the evidence supporting the efficacy and safety for immunomodulatory therapy for steroid-resistant or steroid-dependent ocular inflammatory disease?"

A computer-based (MEDLINE), search of the database from the National Library of Medicine, Bethesda, Maryland, of the literature from 1970 to 2000 on the use of immunomodulatory therapy in non-ocular, non-malignant disease in children, and in the use of immunomodulatory therapy in ocular inflammatory disease in children was conducted. An attempt at analyzing reported side effects, toxicity, and complications was made. Additionally, an analysis of our experience in pediatric immunomodulatory therapy over the past 25 years was performed.

The non-ocular, non-malignant disorders for which immunomodulatory therapy was prescribed which I reviewed included solid organ and bone marrow transplants, rheumatic disorders, vasculitis disorders, including childhood Wegener's granulomatosis, polyarteritis nodosa, and Adamantiades-Behcet's disease, dermatologic disorders, including childhood pemphigus vulgaris and psoriasis, asthma and nephrotic syndrome. Three-thousand, one-hundred and eight publications were reviewed. It became immediately apparent that a variety of impediments to clarity of analysis existed for many of the non-ocular, non-malignant disorders for which immunomodulatory therapy might be prescribed. For example, 1,074 publications on solid organ and bone marrow transplantation were reviewed. But multiple immunomodulatory therapy agents, combined into "recipes" were employed for each patient in each of those publications. Additionally, underlying illness which led to the transplant also confounded the picture. And finally, concurrent use of chronic systemic steroid confused matters.¹⁻¹⁰ Clear data to emerge from this analysis, however, include: major medication induced nephrotoxicity and neurotoxicity was common in children treated with either cyclosporin or with tacrolimus (FK506) for prevention of solid organ transplant or bone marrow transplant rejection or in treatment of nephrosis;^{1,9} infection was relatively common in children treated concomitantly with systemic steroid and an immunosuppressant;⁵ mycophenolate mofetil at 600 mg/m² bid is subtherapeutic (more acute renal allograft rejections) and more toxic than are therapeutically effective doses of azathioprine.⁵

Of the childhood rheumatic diseases assayed (juvenile idiopathic arthritis, systemic lupus erythematosus, relapsing polychondritis, localized scleroderma and polymyositis), the best data emerge from the juvenile idiopathic arthritis (JIA) literature. Two hundred and thirty-three publications on the matter of immunomodulatory therapy for JIA were reviewed. Methotrexate was the immunomodulatory agent used most commonly, by far.¹¹⁻¹⁴ However, publications on the use of cyclosporin, azathioprine, and chlorambucil were also useful.

Ruperto and associates¹¹ studied 132 children with JIA treated with methotrexate, with no reported clinically significant drug-induced complications. Woo and colleagues¹² reported that one of the 27 children with JIA treated with 15-20 mg/m² methotrexate required drug discontinuation secondary to rising liver enzymes after the patient contracted hepatitis A.

Giannini and associates studied 127 children with juvenile idiopathic arthritis, 86 of whom were treated with methotrexate, comparing both efficacy and side effects with an additional 41 children treated with placebo in a double-blind placebo-controlled trial. Only three children treated with methotrexate discontinued therapy because of side effects, and none had significant toxicity. The side effects included gastrointestinal upset and oral mucosal aphthous ulceration. All side effects were graded as either mild or moderate in severity, except for 2 episodes of stomach pain graded as severe in a patient receiving placebo.

Laxer concludes, in his summary on the matter¹⁴ that methotrexate therapy for JIA is the

mainstay of treatment of that disease because of both its efficacy and its safety, pointing out that liver toxicity is very uncommon, as are osteopathy, embryopathy and malignancy, with any even remote association with the latter being controversial and unclear.

Weiss, Wallace, and Sherry, in their 1998 publication, reported on 7 children with steroid-dependent uveitis and cataract and glaucoma, whom they treated with methotrexate, in a dose to 1mg/kg/week given subcutaneously.¹⁵ Uveitis was controlled in six of the seven patients, allowing steroid to be discontinued or at least dramatically reduced. The time to response was 1-4 months. Three of seven patients had rising serum aminotransferase levels during the appropriate monitoring, necessitating dose reduction of the methotrexate; no patient required discontinuation of medication because of complications. Weiss and associates conclude that **early use of methotrexate may allow for complete suppression of JIA-associated uveitis and reduce the cumulative exposure to corticosteroids in refractory cases.**

We had previously reported similar findings and recommendations in a 1992 article, and in an expanded series on 160 patients with uveitis treated with methotrexate;^{16,17} Our data confirmed the safety profile of this drug, and further emphasized its utility in control of uveitis in patients with steroid-dependent uveitis. However, the group of children in whom the highest proportion failed to completely respond to methotrexate were those with juvenile idiopathic arthritis; in this group of patients, 75% responded to this drug, while 25% required the addition of a second agent or a switch to an alternative agent.¹⁷

Good, easily analyzable data could not be obtained from the publications relating to Adamantiades-Bechet's disease, Wegener's granulomatosis, polyarteritis nodosa, Churg-Strauss syndrome, Goodpasture's syndrome, Crohn's disease, pemphigus vulgaris, eczema, psoriasis, epidermolysis bullosa acquisita, asthma, or autoimmune hepatitis.¹⁸⁻²⁶ However, excellent, easily usable data emerged from an analysis of the literature on nephrotic syndrome (see below). Six-hundred and seventy-four publications on the matter of nephrotic syndrome were reviewed. The immunomodulatory agents typically employed in the care of children with frequently relapsing, steroid-dependent nephrotic syndrome included cyclosporin, cyclophosphamide, and chlorambucil. The cyclophosphamide regimens involved in the studies included 5mg/kg/day by mouth, or 75mg/m²/day by mouth for up to 52 weeks. The chlorambucil doses employed in the trials analyzed included 0.2mg/kg/day and 0.3mg/kg/day. The cyclosporin dose employed was 6mg/kg/day.

Analysis of adverse effects in a meta-analysis by Durkan and associates disclosed the following.²⁷ Chlorambucil at 0.3mg/kg/day is highly toxic and frequently associated with unacceptable levels of leukopenia. Cyclosporin at 6mg/kg/day is frequently associated with nephropathy, hypertension, hirsutism, and gum hypertrophy; lesser doses are ineffective for inducing remission in nephrotic syndrome. Therefore, cyclosporin is believed by the authors to be inappropriate for this indication.

The meta-analysis showed that the relative risk for nephrotic syndrome relapse was 0.44 following cyclophosphamide therapy, so that the risk of relapse is reduced from 100% to 40%, i.e., 60 fewer children relapse for each 100 treated. For every 100 treated, one will develop an infection and four will develop cystitis. Therefore, a risk/benefit analysis is highly appropriate before any child is committed to cyclophosphamide therapy. For example, children who relapse only once during the first six months after an initial course of prednisone therapy have only a 10% risk of becoming a frequent relapser, i.e., 10 of 100. Cyclophosphamide therapy would reduce this risk by 60%, and so only 6 of 100 such children would benefit from cyclophosphamide therapy, while the number suffering adverse effects would remain unchanged. Therefore, the risk/benefit ratio would be acceptable only for children with frequently relapsing syndrome. A similar exercise in estimating a risk/benefit ratio in considering steroid-sparing immunomodulatory therapy for children with uveitis is clearly appropriate.

An estimate of the risk/benefit ratio in children with juvenile idiopathic arthritis with dependency on steroid versus moving on to low dose once weekly methotrexate therapy is straightforward. The data on safety and efficacy of methotrexate therapy for this indication are clear, and clearly indicate that the risk/benefit ratio calculation for children whose arthritis is steroid-dependent or treatment-resistant favors moving along to methotrexate immunomodulatory therapy. Similarly, the same estimate of risk versus benefit can be done for children with JIA-associated iridocyclitis. Just as in the case of children with nephrotic syndrome, not every child with JIA-associated iridocyclitis is destined to have a chronic, or recurrent, or conventional-treatment-resistant course. But good data exist regarding prognosticators for identifying patients whose JIA-associated uveitis is more likely than not to be chronic, recurrent, or "stubborn". Kanski and others for example, have suggested that those JIA patients who develop uveitis

prior to the onset of arthritis have a worse prognosis than those in whom arthritis develops first.²⁸ Wolfe and associates attempted to analyze visual prognostic factors in 51 patients with JIA-associated uveitis by dividing their patients into mild or advanced uveitis subgroups. Those who had posterior synechiae and active inflammation at the time of presentation to the ophthalmologist had a worse long-term outcome than did those who had no active inflammation at first evaluation.²⁹ Edelsten and associates³⁰ recently reported on their study of 163 patients with JIA-associated uveitis, in an attempt to evaluate baseline risk factors predictive of severity and chronicity of the uveitis. Like Wolfe, these researchers found that complications and a generally poor outcome were significantly more common in those patients who had uveitis at the time of their initial screening visit with the ophthalmologist. Further, they confirmed the observations of others that the more severe the uveitis was at presentation, the more likely vision-damaging complications would ensue throughout the course of the patient's disease. Our work on this matter,³¹ based on our analysis of 43 patients with JIA-associated uveitis identified those patients referred to Dr. Foster as being comprised of 93% with chronic uveitis, 5% with recurrent uveitis, and 2% with an acute monophasic disease course. The mean overall duration of the uveitis was 146 months, with females suffering from a significantly longer duration of active disease than did males. The female sex, longer duration of uveitis, younger age at uveitis onset, and longer delay between onset of uveitis and presentation to a uveitis subspecialist were associated significantly with visual acuity impairment. The same factors, along with dependence on corticosteroids (lack of treatment with systemic antiinflammatory medication aside from steroids) were correlated strongly with a final visual acuity outcome of less than 20/40. We concluded that earlier case identification and referral to a uveitis specialist trained and prepared to engage in immunomodulatory therapy of such patients had the best chance of minimizing the likelihood of visual impairment in patients with JIA-associated uveitis. Therefore, the 12-year-old boy who is HLA-B27 negative, ANA negative, with oligoarticular juvenile idiopathic arthritis who has 2 or 3 mild episodes of anterior uveitis clearly should not be advanced to methotrexate immunomodulatory therapy for care of his eye disease. On the other hand, such a patient with severe uveitis at the outset, which is still requiring topical with or without regional injection or systemic steroid 6 months after the first visit to the ophthalmologist should seriously be considered for advancement to methotrexate. Similarly, the 2-year-old female who is ANA positive with oligoarticular arthritis, found on initial screening examination to have significantly impaired visual acuity in one eye, with posterior synechiae in both eyes and a significant cataract in one eye should almost certainly be seriously considered for methotrexate therapy almost immediately.

The meta-analysis study by Latta and associates³² analyzed 38 studies involving 1504 children and 1573 courses of cytotoxic drug therapy. The regimens involved in those 38 studies included cyclophosphamide at a dose of 2-5mg/kg/day or chlorambucil at 0.1-0.2mg/kg/day.

Leukopenia was common, but generally as a desired "side effect" of effective alkylating therapy. Infection developed in 1.5% of patients on cyclophosphamide, but in 6.3% of patients receiving chlorambucil. Additionally, 0.2% of patients on cyclophosphamide developed a malignancy, while 0.6% of patients on chlorambucil therapy did so. Three percent of patients on chlorambucil therapy developed a seizure disorder, and 2.2% of patients on cyclophosphamide developed cystitis.

The authors conclude that the margin between effective treatment and a dose toxic to the patient is too narrow for chlorambucil, and that therefore cyclophosphamide is the preferred therapy for steroid-dependent, frequently relapsing nephrotic syndrome.

Additional matters of significant interest to us within ophthalmology confronted by the need to decide about alkylating therapy are gonadal toxicity and secondary malignancy. Guesry concludes that the margin between effective treatment and a dose toxic to the gonads was smaller with chlorambucil than with cyclophosphamide.³³ He estimates that 17mg/kg chlorambucil cumulative dose with concurrent steroid use is safe for the gonads of males, while 200mg/kg of cyclophosphamide could be used safely. The gonadal toxicity of cytotoxic therapy was less severe in females than in males in his study, and pregnancies had been reported after cumulative doses of up to 525mg/kg of cyclophosphamide and after up to 28mg/kg for chlorambucil.

Nephrotic syndrome has been associated with lymphoma, and 2 children with nephrotic syndrome without cytotoxic therapy have had leukemia. Therefore, attributing malignancy in nephrotic syndrome treated with immunomodulatory therapy is complicated. Fourteen of 1504 children reported in the meta-analysis of Latta et al³² developed a malignancy, and some of the malignancies were ones that one would not traditionally associate with being a consequence of alkylating therapy.

Additionally, in some of the cases, the doses of alkylating agent had been quite low, calling into

question the relationship between the alkylating therapy and the malignancy. But it seems clear that a relationship can exist, and, further, that the higher the cumulative dose, the more likely a leukemia may develop. Chlorambucil, in particular, has been associated with leukemia. But at the doses and durations typically employed in children with ocular inflammatory disease, this appears not to be a significant issue.

Latta et al recommend that the criteria for treating children with nephrotic syndrome with cytotoxic therapy should include a frequently relapsing nature of the nephrotic syndrome, the development of steroid toxicity, such as cataract and growth failure and Cushingoid status, and/or the development of psychological complications from the use of steroid.³² Cyclophosphamide is preferred over chlorambucil, with oral cyclophosphamide at a dose of 2-3mg/kg/day, keeping the white count above 3000 cell/m³, and employing alternative day steroid concomitantly. Latta suggests aiming for less than 300mg/kg cumulative dose in males.³²

Pulse intravenous cyclophosphamide therapy may, in fact, be the best approach of all in this setting of frequently relapsing nephrotic syndrome. Gulati et al reported on this strategy of treating 51 children with steroid-dependent, frequently relapsing nephrotic syndrome.³⁴ The mean age of the children was 4 years, and the dose employed was 500mg/m²/month for six months, with a 5-year follow up. The authors concluded that this is a safe and effective way of administering alkylating therapy, comparable in efficacy to oral daily cyclophosphamide, with 40% less cumulative dose, and therefore fewer side effects. The side effects included nausea and vomiting at the time of infusion (5%), alopecia (8%), leukopenia (4%), pneumonitis (2%), and infection (2%). No patient discontinued therapy due to a side effect. Mok et al similarly extol the virtues of pulse intravenous cyclophosphamide in their care of children with diffuse proliferative lupus glomerulonephritis.³⁵ They studied 55 patients, 22 receiving intravenous cyclophosphamide and 33 receiving oral cyclophosphamide. The patients receiving IV pulse cyclophosphamide never developed cystitis, whereas 5% of the patients receiving oral cyclophosphamide did. Half the menstruating females on oral cyclophosphamide developed oligomenorrhea, whereas only 25% of those receiving IV pulse cyclophosphamide did.

Finally, Lehman and Onel additionally speak to the matter of intermittent intravenous pulse cyclophosphamide in the care of children with systemic lupus erythematosus nephritis.³⁶ Sixteen children with systemic lupus erythematosus associated glomerulonephritis were treated with intravenous pulse cyclophosphamide for 36 months. The regimen involved a dosage of 500-750mg/m² monthly for six months, followed by that same dose every 3 months for the succeeding 30 months. Side effects included nausea during the infusion (this was typically controllable and necessitated no change in therapy) alopecia (none to the extent of complete baldness), and leukopenia (an inescapable and, frankly, essential "side effect" from cyclophosphamide therapy, without which the therapeutic effect will never be achieved). No child withdrew from therapy during the entire course of treatment, no instances of cystitis were encountered, no female reaching pubescence developed amenorrhea, and no patient has developed a malignancy.

Rosenbaum³⁷ applied this approach, but at reduced dose, for 11 adults with steroid-resistant uveitis, reporting that five of the 11 benefited from this approach. We, on the other hand, have been very impressed at both the safety and the efficacy of intravenous pulse cyclophosphamide therapy in the care of patients whose uveitis has failed to adequately respond not only to systemic and regional steroid therapy, but has also failed to remit with more conventional, orally administered immunomodulatory agents, such as methotrexate, cyclosporin, azathioprine and mycophenolate mofetil.³⁸

CONCLUSIONS

Abundant reliable published evidence exists in the world's peer-reviewed literature attesting to the safety of several immunomodulatory agents for treating both ocular and systemic non-malignant inflammatory disease. Some agents are clearly safer than others. For example, methotrexate has an extraordinary safety record in the care of patients with such disorders. Cyclosporin is more toxic in children at therapeutic doses. Mycophenolate mofetil, an immunomodulatory agent quite useful in the care of adults with ocular inflammatory disease^{39,40} is more toxic to children than is azathioprine or methotrexate.³ Cyclophosphamide, particularly given in the intravenous pulse mode, is clearly superior, at least from a safety standpoint, to daily oral cyclophosphamide and to daily oral chlorambucil.

RECOMMENDATIONS

1. Ophthalmologists should acquaint themselves with the literature references herein. Ophthalmologists should acquaint themselves with the evidence-based medicine recommendations of the American Uveitis Society regarding the wisdom of immunomodulatory therapy for specific ocular

inflammatory disorders.⁴¹

2. Ophthalmologists should acquaint themselves with the recommendations of the International Uveitis Study Group on this matter as well, with specific reference to the disorders and situations in which this Society considers the use of immunomodulatory agents mandatory.⁴²

3. The American Academy of Ophthalmology should publish Preferred Practice Guidelines which highlight these findings and the recommendation of these two specialty groups.

4. Chairmen of Departments of Ophthalmology should recruit to their faculties ocular immunologists who have been specifically trained to care for patients, including children with uveitis, in ways consistent with the principles promoted by the American Uveitis Society and by the International Uveitis Study Group, not only to deliver such care, but also to ensure that succeeding generations of residents in training in ophthalmology will be better educated about the safety and indications for such therapy and about the collaborative strategies they may employ effectively with chemotherapists prepared to take responsibility for the details of prescribing and monitoring such therapy.

REFERENCES

1. Nash RA, Anton JH, Karanes C, et al. Phase III study comparing methotrexate and tacrolimus with methotrexate and cyclosporin for prophylaxis of acute graft-versus-host disease after marrow transplantation from unrelated donors. *Clin Obs Interv Therapeut Trials* 2000;96:2062-8.
2. Pappas PA, Wepler D, Pinna AD, et al. Sirolimus in pediatric gastrointestinal transplantation: the use of sirolimus for pediatric transplant patients with tacrolimus-related cardiomyopathy. *Pediatr Transplant* 2000;4:45-49.
3. Zuckermann A, Klepetko W, Birsan T, et al. Comparison between mycophenolate mofetil and azathioprine-based immunosuppressions in clinical lung transplantation. *J Heart Lung Transplant* 1999;18:432-40.
4. Vester U, Kranz B, Testa G, et al. Efficacy and tolerability of interleukin-2 receptor blockade with basiliximab in pediatric renal transplant recipients. *Pediatr Transplant* 2001;5:297-301.
5. Virga M, Carter JE, Lirenman DS. Single-center experience with mycophenolate mofetil in pediatric renal transplant recipients. *Pediatr Transplant* 2001;5:293-6.
6. Jacqz-Aigrain E, Shaghaghgi EK, Baudouin V, et al. Pharmacokinetics and tolerance of mycophenolate mofetil in renal transplant children. *Pediatr Nephrol* 2000;14:95-99.
7. Roberti I, Reisman LA. A comparative analysis of the use of mycophenolate mofetil in pediatric versus adult renal allograft recipients. *Pediatr Transplant* 1999;3:231-5.
8. Benfield MR, Stablein D, Tejani A. Trends in immunosuppressive therapy: a report of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS). *Pediatr Transplant* 1999;3:27-32.
9. Seikaly MG, Prashner H, Nolde-Hurlbert B, Browne R. Long-term clinical and pathological effects of cyclosporin in children with nephrosis. *Pediatr Nephrol* 2000;14:214-7.
10. Houtenbos I, Bracho F, Davenport V, Slack R, van de Ven C, Suen Y, Killen R, Shen V, Cairo MS. Autologous bone marrow transplantation for childhood acute lymphoblastic leukemia: a novel combined approach consisting of ex vivo marrow purging, modulation of multi-drug resistance, induction of autograft vs leukemia effect, and post-transplant immuno- and chemotherapy (PTIC). *Bone Marrow Transplant* 2001;27:145-53.
11. Ruperto N, Ravelli A, Falcini F, et al. Responsiveness of outcome measures in juvenile chronic arthritis. Italian Pediatric Rheumatology Study Group. *Rheumatol* 1999;38:176-180.
12. Woo P, Southwood TR, Prieur AM, et al. Randomized placebo-controlled, cross-over trial of low-dose oral methotrexate in children with extended oligoarticular or systemic arthritis. *Arthritis Rheum* 2000;43:1849-57.
13. Giannini EH, Brewer EJ, Kuzmina N, et al. Methotrexate in resistant juvenile rheumatoid arthritis. Results of the U.S.A. ¶ U.S.S.R. double-blind, placebo-controlled trial. *N Engl J Med* 1992;326:1043-9.
14. Laxer RM. Long-term toxicity of immune suppression in juvenile rheumatic diseases. *Rheumatol* 1999;38:743-6.
15. Weiss AH, Wallace CA, Sherry DD. Methotrexate for resistant chronic uveitis in children with juvenile rheumatoid arthritis. *J Pediatr* 1998;133:266-8.
16. Hemady RK, Baer JC, Foster CS. Immunosuppressive Drugs in the Management of Progressive, Corticosteroid-Resistant Uveitis Associated with Juvenile Rheumatoid Arthritis. *Int Ophthalmol Clin* 1992;32:241-252.

17. Samson CM, Waheed NK, Baltatzis S, Foster CS. Methotrexate Treatment of Uveitis. *Ophthalmology* 2001;108:1134-9.
18. Bunikowski R, Staab D, Kussebi F, et al. Low-dose cyclosporin A microemulsion in children with severe atopic dermatitis: clinical and immunological effects. *Pediatr Allergy Immunol* 2001;12:216-23.
19. Kili SŞ, Hacimustafaoglu M, Celebi S, et al. Low dose cyclosporin A treatment in generalized pustular psoriasis. *Pediatr Dermatol* 2001;18:246-8.
20. Vrugt B, Wilson S, Brawn A, et al. Low dose methotrexate treatment in severe glucocorticoid-dependent asthma: effect on mucosal inflammation and in vitro sensitivity to glucocorticoids of mitogen-induced T cell proliferation. *Eur Respir J* 2000;15:478-85.
21. Piraccini BM, Tosti A, Iorizzo M, Misciali C. Pustular psoriasis of the nails: treatment and long-term follow-up of 46 patients. *Br J Dermatol* 2001;144:1000-5.
22. Reitamo S, Spuls P, Sassolas B, et al. Efficacy of sirolimus (Rapamycin) administered concomitantly with a subtherapeutic dose of cyclosporin in the treatment of severe psoriasis: a randomized controlled trial. *Br J Dermatol* 2001;145:438-45.
23. Wananukul S, Pongprasit P. Childhood pemphigus. *Int J Dermatol*. 1999;38:29-35.
24. Bakkaaloglu SA, Ekinu M, Tamer N, et al. Severe renal impairment in the case of classic polyarteritis nodosa. *Pediatr Nephrol* 2001;16:148-50.
25. Stegmayr BG, Gothefors L, Malmer B, et al. Wegener granulomatosis in children and young adults. A case study of ten patients. *Pediatr Nephrol* 2000;14:208-13.
26. Kari JA, Shah V, Dillon MJ. Behçet's disease in U.K. children: clinical features and treatment including thalidomide. *Rheumatol* 2001;40:933-8.
27. Durken AM, Hodson EM, Willis NS, Craig JC. Immunosuppressive agents in childhood nephrotic syndrome: a meta-analysis of randomized controlled trials. *Kidney Int* 2001;59:1919-21.
28. Kanski JJ. Juvenile arthritis and uveitis. *Surv Ophthalmol* 1990;34:253-67.
29. Wolfe MD, Lichter PR, Ragsdale CG. Prognostic factors in the uveitis of juvenile rheumatoid arthritis. *Ophthalmology* 1987;94:1242-7.
30. Edelsten C, Lee V, Bentley CR, et al. An evaluation of baseline risk factors predicting severity in juvenile idiopathic arthritis associated uveitis and other chronic anterior uveitis in early childhood. *Br J Ophthalmol* 2002;86:51-6.
31. Dana MR, Merayo-Llodes J, Schaumburg DA, Foster CS. Visual outcomes prognosticators in juvenile rheumatoid arthritis-associated uveitis. *Ophthalmology* 1997;104:236-44.
32. Latta K, von Schnakenburg C, Ehrich J. A meta-analysis of cytotoxic treatment for frequently relapsing nephrotic syndrome in children. *Pediatr Nephrol* 2001;16:271-82.
33. Guesry P, Lenoir G, Broyer M. Gonadal effects of chlorambucil given to prepubertal and pubertal boys for nephrotic syndrome. *J Pediatr* 1978;92:299-303.
34. Gulati S, Pokhariyal S, Sharma RK. Pulse cyclophosphamide therapy in frequently relapsing nephrotic syndrome. *Nephrol Dial Transplant* 2001;16:2013-7.
35. Mok CC, Ho CT, Siu YP, et al. Treatment of diffuse proliferative lupus glomerulonephritis: a comparison of two cyclophosphamide containing regimens. *Am J Kidney Dis* 2001;38:256-64.
36. 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.
37. Rosenbaum JT. Treatment of severe refractory uveitis with intravenous cyclophosphamide. *J Rheumatol* 1994;21:123-5.
38. Durrani K, Foster CS. IV pulse cyclophosphamide therapy in ocular inflammatory disease: efficacy and outcomes. *Ophthalmology* 2002. Submitted for publication
39. Larkin G, Lightman S. Mycophenolate mofetil. A useful immunosuppressive in inflammatory eye disease. *Ophthalmology* 1999;106:370-4.
40. Tufail F, Yu EN, Foster CS. Mycophenolate mofetil as an immunomodulatory agent in the treatment of chronic ocular inflammatory disorders. *Ophthalmology* 2002. Submitted for publication
41. Jabs DA, Rosenbaum JT, Foster CS, et al. Guidelines for the use of immunosuppressive drugs in patients with ocular inflammatory disorders: recommendation of an expert panel. *Am J Ophthalmol* 2000;130:492-513.
42. Rao NA, Blackman HJ, Franklin RM, et al. Basic and clinical science course, Section 9, American Academy of Ophthalmology, 1998-1999. Page 77-78. Table 1-9.

