down this road the very best of luck!

G.S. DEAN, *PhD, Post-doctoral scientist*
D.A. ISENBERG, *MD, ARC Diamond Jubilee Professor of Rheumatology, UCL*

Department of Immunology, University College London Medical School, Windeyer Building, 46 Cleveland Street, London W1P 6DB, UK.

References

1. DEAN GS, ISENBERG DA: Detection of anti-cardiolipin antibodies in culture supernatants. *Clin Exp Rheumatol* 2001; 19: 251-7.
2. TINCANI A, MERONI PL: Anticardiolipin antibodies: To be or not to be detectable. *Clin Exp Rheumatol* 2001; 19: 240-1.

Combining cyclosporine with prevailing antirheumatic drug therapy in the treatment of juvenile idiopathic arthritis

Sirs,

The effect of cyclosporine either alone or in combination with various disease modifying antirheumatic drugs (DMARD), mainly methotrexate, has been shown in rheumatoid arthritis (1). However, there is little data on the effect of cyclosporin in the treatment of juvenile idiopathic arthritis (JIA) and they have mainly focused on the systemic onset type of the disease (2). There are no studies which have assessed the effect of a combination of cyclosporine with other DMARDs in JIA. We retrospectively analysed the usefulness of adding cyclosporine to the treatment protocol in 32 children (27 girls and 5 boys) with active JIA resistant to conventional DMARD therapy, which in all cases included methotrexate. The mean (SD) age of the patients was 9.1 (± 2.8) years. The onset type of the disease was: extended oligoarthritis (n=6), oligoarthritis (n=4), polyarthritis (n=19) and systemic onset JIA (n=3). Fourteen patients had iritis at the onset of cyclosporine treatment.

After the onset of cyclosporine treatment most patients continued to use their earlier DMARD combination including methotrexate in every case. Cyclosporine plus methotrexate was combined with two other DMARDs in 6 patients, with one DMARD in 16 patients, and 10 patients had a simple cyclosporine plus methotrexate combination. The drugs in the combinations were methotrexate (n=32), natrium aureothiomalate (n=2), sulfasalazine (n=8), hydroxychloroquine (n=17), and azathioprine (n=1). The prevailing drug therapy remained stable, and we did not include in this analysis patients in whom the DMARD therapy had been changed. At the onset of cyclosporine treatment, the mean starting dose of methotrexate was 20.1 mg/week in the 14 patients who used it *per os* and 21.4 mg in the 18 patients who received it parenterally. The mean initiating dose of cyclosporine was 2.5-3 mg/kg/day. Sixteen (50%) out of the 32 patients took cyclosporine for at least two years. Side effects were monitored following good clinical practice with special attention devoted to blood pressure and renal function, measured by the level of serum urea, and by the creatinine clearance test in cases with a suspicion of impaired renal function.

For this study the effect of treatment and the side effects were checked from the medical records up to 2 years from the onset of the treatment. The treatment effect was assessed as a change in hospitalisation days and in prednisolone dose, and by the common inflammatory indexes, i.e. the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Our treatment policy includes treating all clinically active joints with intra-articular corticosteroids. Thus, for this retrospective study we also considered the change in the number of active joints as an outcome measure of disease activity. The data were assessed by intention-to-treat (ITT) analysis after to years from the onset of cyclosporine treatment. The last observation carried forward (LOCF) was used when there were missing clinical and laboratory data.

Table I shows our main results. Both ESR and CRP showed a significant reduction, while there was a significant increase in the need for hospitalisation and for intra-articular corticosteroid injections. One patient with polyarthritis had a remission after 6 months which lasted up to the two-year check-up. Side effects were frequent but usually mild or reversible, and did not require in any case the cessation of the therapy. In 2 cases with iritis the signs of inflammation totally disappeared; in one of them, however, the follow-up had lasted only one year. In addition,6 patients initially showed improvement in their iritis, but this was restricted to the first 6-month period.

In conclusion,this series represented active, severe cases of JIA who were aggressively treated with various DMARD combinations without achieving disease control. In all cases we added cyclosporine to the prevailing drug therapy which included methotrexate. After adding cyclosporine to the prevailing DMARD combination there was a significant reduction in laboratory indexes of inflammation. On the other hand, there was an increase in the number of intra-articular corticosteroid injections needed and in the number of hospitalisation days. Moreover, spontaneous fluctuations in different factors that represent disease activity can modify the result. Overall our results are based on retrospective data and must be considered preliminary. Though all of the patients had methotrexate and cyclosporine as a minimum combination, 2/3 of the patients in the series had additional DMARDs which invalidizes the analysis as to a given drug combination. Mild side effects were frequent, but adverse effects were not seen. We are awaiting controlled studies on this important topic.

Table I. Outcome in 32 JIA patients after adding cyclosporine to the prevaling DMARD treatment.

Variable	Baseline Median (IQR)	At 24 months Median (IQR)	Median change[3] Median (95% CI)	p-value[4]
Hospitalisation days[1]	5.5 (4.0, 7.5)	9 (4, 15)	4 (0.5 to 7.0)	0.040
Prdn, dose, mg[2]	10.0 (7.5, 15.0)	10 (7.5, 17.0)	0 (-2.5 to 2.5)	0.82
GC injections[1], n	3 (1.5, 5.0)	4.5 (2, 8)	2 (0.5 to 4.0)	0.022
ESR, mm/h	36 (18, 52)	20 (12, 36)	-10 (-1.5 to -22.0)	0.012
CRP, mg/l	27 (5, 71)	2 (0, 12)	-28 (-8.0 to -40.5)	< 0.001
fS-urea mg/l	3.8 (3.2, 4.6)	4.2 (3.6, 5.5)	0.5 (-1.0 to 1.2)	0.088

[1]Calculated within 3-month periods; [2]Every other day; [3]Rank-based confidence interval for difference in paired medians; [4]Kornbrot's rank difference test. IQR = interquartile range.

J. HAAPASAARI, *MD*
H. KAUTIAINEN, *Biostatistician*
M. HAKALA, *MD*

Rheumatism Foundation Hospital, FIN-18120 Heinola, Finland.
Address correspondence to: Dr. Jarkko Haapasaari, jarkko.haapasaari@reuma.fi fax +358-3-8491298.

References

1. STEIN M,PINCUS T: Combination treatment of rheumatoid arthritis with cyclosporine and methotrexate. *Clin Exp Rheumatol* 1999; 17 (Suppl. 18): S47-52.
2. GERLONI V, CIMAZ R,GATTINARA M,ARNOLDI C, PONTIKAKI I, FANTINI F: Efficacy and safety profile of cyclosporin A in the treatment of juvenile chronic idiopathic arthritis. Results of a 10-year prospective study. *Rheumatology* 2001; 907-13.