## Efficacy of cyclosporine as a single agent therapy in chronic idiopathic thrombocytopenic purpura

We read with interest the letter by Emilla *et al.*[1] describing long-term results of low dose cyclosporine in idiopathic thrombocytopenic purpura (ITP). It would have been interesting to know in how many patients was cyclosporine used so that the overall response rates could be known. There are anecdotal reports using Cyclosporin for chronic ITP with various doses.[1-7] The overall response to cyclosporine was found in 40-55% of patients. Many patients remained dependent on cyclosporine. We would like to share our experience of therapy with cyclosporine in a large cohort of patients with chronic ITP in both adults and children.

Patients and method: This study is a prospective study of chronic ITP patients treated with cyclosporine at our centre from July 2004 to December 2005. The diagnosis of ITP was based on the presence of thrombocytopenia with normal or increased megakaryocytes in a morphologically normal marrow. Inclusion criteria were: Patients with platelet counts < 30,000/uL or more if they were bleeding, normal renal and liver function, failure of treatment with steroid, splenectomy, or other drugs. Cyclosporine was given as a single agent. Patients were also off another therapy for at least 2 weeks prior to trial. Secondary causes of thrombocytopenia such as systemic lupus erythematosus, lymphoproliferative disorders and HIV infection was excluded.

Cyclosporin was used in the dose of 5 mg/kg/d in two divided doses for 1 week and then reduced to 3 mg/kg/d to maintain serum level between 200-400 ng/mL. Follow-up was done biweekly with platelets counts, liver and renal function test. In patients with response, cyclosporin was continued for period of 6 months and cyclosporin was stopped in patients failing to respond at the end of 3 months. Complete response (CR) was defined as platelet counts of >100x10$^9$/L or more for at least 2 months; partial response (PR) defined as doubling of platelet counts from initial level and more than 50x10$^9$/L for at least 2 months and no response if platelets counts remained less than 50x10$^9$/L.

### Statistical analysis

Data analysis was done using SPSS version 10.0. $p$<0.05 were considered as statistically significant.

### Results

A total of 25 patients (15 males: 10 females) were enrolled. The median age was 12 years (range 4-73 years). Fifteen patients were less than 18 years old. At the time of enrollment median duration of ITP was 24 months (6 months to 90 months).

All patients had skin bleed, 16 patients (64%) had mucosal bleed, and 4 patients (16%) had gastrointestinal bleed, 3 patient (12%) had hematuria and one patient (4%) presented with intracranial haemorrhage. Of the ten females, 4 presented with menorrhagia.

Table 1. Response to cyclosporine in relation to previous therapy.

| *Medicines used before cyclosporine therapy* | *Total Number of patients (n=25)* | *NR* | *PR* | *CR* | *Overall responses (CR+PR)* |
|---|---|---|---|---|---|
| P | 15 | 7 | 2 | 6 | 32% |
| P + D | 3 | 3 | 0 | 0 | 0 |
| P + IVIg | 3 | 1 | 0 | 2 | 8% |
| P + AD | 1 | 1 | 0 | 0 | 0 |
| P + IVIg + D | 1 | 0 | 0 | 1 | 4% |
| P + IVIg + S | 1 | 1 | 0 | 0 | 0 |
| P + S + D + Dz (p=0.41) | 1 | 1 | 0 | 0 | 0 |

AD-anti D, D-dapsone, Dz-danazol, IVIg-intravenous gammaglobulin, P-prednisone, S-splenectomy.

All patients were treated with oral prednisone with transient response in four patients before starting cyclosporine therapy. In addition to prednisone, 5 patients received intravenous gamma globulin with transient response in one, 2 patients had undergone splenectomy without any response, 1 patient received danazol without any response, and 6 patients received dapsone with transient response. Previous therapies received by patients are shown in Table 1. Before starting cyclosporin all patients were subjected to complete renal and liver function test. Blood pressure was monitored before therapy and during study group. Median base line platelets counts were 18x10$^9$/L (2-42x10$^9$/L). Median hemoglobin was 119 g/L (84-143 g/L, total leukocyte counts were 10.1x10$^9$/L (4.5-19.9x10$^9$/L). All six patients with platelet counts of >30x10$^9$/L were having mucocutaneous bleeding.

The overall responses were seen in 11 patients (44%). Complete response (CR) was seen in 9(36%) patients and partial response (PR) was seen in 2 patients (8%). Patients <18 years showed 16% response rates (3CR+1PR). There was no correlation of response to pretreatment platelets counts, or duration of ITP before starting therapy with cyclosporine, or refractoriness of ITP to number of treatment modality. Mean follow-up period of patients with response was 7.3±2.1 months.

Three patients relapsed on therapy with cyclosporine. One patient developed fatal ICH after relapse and died. Gingival hyperplasia was seen in 2 patients. We did not observe hypertension or hirsutism in this cohort in the prescribed doses.

### Discussion

The responses to cyclosporin in chronic ITP were observed from 40-55% in published studies of patients with small numbers 2-6. Present study is largest study using cyclosporin as a treatment for refractory ITP. In present study, an overall response of 44% was observed in refractory ITP patients using low dose of cyclosporin; 36%

patients achieved CR and 8% of patients developed PR.

Present study also suggests that cyclosporine may not be an effective agent for children at low doses. An overall response of 16% (4/25) was observed in refractory ITP children in this cohort. Perrotta *et al.*[2] used higher doses of cyclosporine (10 mg/kg/d) and observed an overall response in 4/14 (28%) children with severe toxicity in 6 patients.

Three patients with response developed relapse on therapy; one patient developed fatal ICH after relapse and expired. We agree with Emilla *et al.*[1] that toxicity of cyclosporine is less at low doses but it may possibly be reducing the response rates also.

In present study, no pre treatment characteristics – sex, age, platelet counts or duration of ITP were correlated with response to cyclosporin. We conclude that cyclosporine may be a suitable alternative in selected relapsed refractory patients of ITP.

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## References

1. Emilia G, Luppi M, Morselli M, Forghieri F, Potenza L, Torelli G. A possible role for low-dose cyclosporine in refractory immune thrombocytopenic purpura (ITP). Haematologica 2008 doi: 10.3324/haematol.12741.
2. Perrotta S, Amendola G, Locatelli F, Conte ML, Rossi F, d'Urzo G, Nobili B. Treatment with short-term, high-dose cyclosporin A in children with refractory chronic idiopathic thrombocytopenic purpura. Br J Haematol 2003;121: 143-7.
3. Zver S, Zupan IP, Cernelc P. Cyclosporin A as an immunosuppressive treatment modality for patients with refractory autoimmune thrombocytopenic purpura after splenectomy failure. Int J Hematol. 2006; 3:238-42.
4. Kappers-Klunne, M.C. & Van't Veer, M.B. Cyclosporin A for the treatment of patients with chronic ITP refractory to corticosteroid or splenenctomy. Br J Haematol.2001;114:121-5.
5. Gesundheit B, Cividalli G,Freeman A, Yatziv S, Koren G, Baruchel S. Cyclosporin A in the treatment of refractory immune thrombocytopenia purpura in children. Eur J Haematol 2001;66: 347-51.
6. Moskowitz IP,Gaynon PS, Shahidi NT, Cripe TP. Low-dose cyclosporin A therapy in children with refractory immune thrombocytopenic purpura. J Pediatr Hematol Oncol 1999; 21: 77-9.
7. Kelsey PR, Schofield KP and Geary CG. Refractory idiopathic thrombocytopenic purpura treated with cyclosporine. Br J Haematol 1985;60:197-8.