

## Cyclosporin A Monotherapy in Young Indian Aplastic Anaemia Patients

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Immunosuppression is the most effective treatment for patients with aplastic anaemia (AA), except for bone marrow transplantation. This may be because immune mediated stem cell suppression appears to be an important pathogenic mechanism in many patients with AA. The mechanism of action of immunosuppressives in AA is unknown. However, they may reverse abnormal immune mediated suppression of hematopoiesis or induce growth and differentiation of marrow stem cells through activation of growth factors or various cytokines. The best results are achieved with antithymocyte globulin and cyclosporin when used with corticosteroids. Few studies have shown that the hematologic response to antithymocyte globulin is poorer in young patients<sup>1</sup>. Several studies have shown that cyclosporin A (CyA) could be effective treatment for AA. However, adequate data concerning immunosuppressive therapy, especially the use of CyA in patients of AA are not available from India. We carried out an open labelled prospective evaluation of efficacy and safety of CyA in young patients with AA.

### MATERIAL AND METHOD

Patients of AA (bone marrow proven) attending haematology clinic of Internal Medicine, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh who were not suitable or unable to afford bone marrow transplantation or who were excluded from antithymocyte globulin therapy because of poor response seen in young age were recruited in the study. Written informed consent was taken before enrollment. Fifteen patients were enrolled from July 1998 to Feb 1999. These included 11 males and 4 females. A detailed physical examination was done to rule out any active infection before start of CyA therapy. Baseline investigations included haemogram, liver function tests, renal function tests, HIV, HBsAg and chest x-ray. All patients were followed up once in two weeks and detailed physical examination as outlined in Table 1 was carried out. During each investigation, patients were closely followed regarding occurrence of side effects. Baseline investigations eg, haemoglobin, TLC, platelets, urea, creatinine, SGOT/SGPT and alkaline phosphatase were also monitored once in two weeks. Patients were initially started on CyA 5 mg/kg/day (Panimun Bioral - CyA oral solution USP 100mg/ml - modified) in twice daily dosages. If there was no response in one month, CyA dose was increased to 7.5 mg/kg/day. A response to therapy was considered if there was an increase in baseline haemoglobin, TLC and platelets or decreases in the requirement of blood transfusions as compared to the state before starting CyA therapy. The blood CyA levels were monitored once in two weeks. Patients were asked to report if they developed any bleeding tendencies, fever or any other side effect immediately to the hospital.

### RESULTS

Out of 15 patients, 3 patients died within 2 weeks of starting CyA because of bleeding complications and septicaemia. Two patients did not report back after one week of starting CyA. Four patients (30.8%) showed response through increase in haemoglobin, TLC, platelets and decrease in blood transfusion requirements. Two additional patients showed partial response through decrease in the number of blood transfusions as compared to pre-CyA therapy state. Four patients did not respond after 12 weeks of therapy and were withdrawn from the study. The mean CyA blood levels were  $142.1 \pm 85.5$  ng/ml as measured by a validated radio immuno assay. There was no significant increase in blood pressure in any patient. The liver function and renal function tests did not show any significant change from the baseline. The most common side effect was gum hyperplasia in two patients (7.7%). CyA was well tolerated among all patients.

## DISCUSSION

AA is a fatal haematologic disorder whose aetiology is not yet clearly defined. The dosage recommendations of CyA in these patients have also not been clearly formalised but it appears that an initial oral CyA dosage of 5 mg/kg/day adjusted according to response and serum creatinine levels is effective. CyA should be continued for at least 3 months and until peripheral red cell counts have stabilised for at least 1 month and then gradually tapered<sup>2</sup>. Eighty four per cent full haematological response in 9-46 months has been reported by Totterman *et al*<sup>3</sup> after using CyA alone or in combination with prednisolone. In severe aplastic anaemia resistant to conventional immunosuppression the response rate is lower but a small proportion (around 15%) may benefit from CyA therapy but longer treatment periods may however be needed to evaluate the role of CyA in AA<sup>3</sup>. With supportive measures using anabolic steroids and low dose steroids 20-50% patients with severe AA die within 6 months to 1 year after diagnosis<sup>4,5,6</sup> and only 10-20% survive with persisting haematologic abnormalities. The most definitive therapy has been the use of immunosuppressive agents including antithymocyte globulin, CyA and cyclophosphamide which yield a variable response ranging from 20-80%<sup>5</sup>. There is however no solid basis to understand the effect of CyA but reports of increased release of immune interferon from the mononucleated leucocytes of patients with severe AA and the well known blocking effect of immune interferon by CyA might provide some explanation in the future<sup>7,8</sup>. Our CyA response rate of (30.8%) at 5-7.5 mg/ kg, for >12 week treatment in young patients has been useful in reducing the severity of the disease as well as the number of blood transfusions. A low CyA side effect profile indicates that CyA was well tolerated by patients and did not add to the severity of disease.

SN	Name	Age	Sex	Start of therapy			End of therapy			*Comments	Side effects
				Hb g%	TLC (/mm <sup>3</sup> )	Platelets (/mm <sup>3</sup> )	Hb (g%)	TLC (/mm <sup>3</sup> )	Platelets (/mm <sup>3</sup> )		
1	IS	18	M	3.9	800	34000	-	-	-	1	-
2	TS	28	F	4.3	1600	11000	-	-	-	2	-
3	V	24	M	4.6	5260	1000	2.6	2230	0	3	Gum hyperplasia
4	GC	19	M	3.7	1850	5000	7.4	4000	10000	4	-
5	AK	16	M	3.0	2500	7000	4.2	3600	4000	5	-
6	MB	14	F	4.8	1430	4000	-	-	-	1	-
7	RK	21	M	4.2	1900	6000	-	-	-	6	-
8	SK	18	M	3.6	3900	9000	4.8	3700	10000	5	-
9	B	15	M	2.0	4200	6000	4.3	5300	12000	4	-
10	RK	25	F	3.4	2100	5000	6.0	2300	15000	4	-
11	S	26	M	2.7	1800	5000	7.6	3900	22000	4	Gum hyperplasia
12	PP	35	M	5.2	1900	23000	4.3	1650	0	3	-
13	SK	26	M	9.7	4020	4000	6.2	4200	7000	3	-
14	R	8	F	6.9	1900	12000	4.9	2100	11000	3	-
15	UA	34	M	4.5	2300	12000	-	-	-	2	-

1-Patient died within one week, 2-Patient lost to follow up, 3-No Response, 4-Responded, 5-Partial Response, 6-Died after two weeks

## CONCLUSION

The efficacy of CyA in the treatment of patients with AA resulted in 30.8% full remittance and 15.8% partial response at 12 weeks of monotherapy.

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