Asian Pacific Journal of Allergy and Immunology (1986) 4:29-32

Methylprednisolone Treatment in Aplastic Anaemia

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SUMMARY **Twenty patients with aplastic anaemia were treated with a short term bolus of methylprednisolone. Seven patients were refractory to anabolic steroids and were observed in very long follow- up periods of 14-104 months. Thirteen patients had never been treated. The latter group also received anabolic steroids. Five out of 20 patients responded to the treatment while the remaining patients did not or died. Responders among patients refractory to anabolic steroids had shorter duration of disease compared to non-responders. No recurrence of aplasia was observed in all responders.**

Aplastic anaemia (AA) is a form of bone marrow failure characterised by blood pancytopaenia with marrow hypocellularity. AA appears to be more prevalent in the orient than in the United States and Europe.[1] In Thailand, in the Department of Medicine, Siriraj Hospital alone, 60-80 new cases of AA are seen annually. Patients with AA present symptoms of anaemia, infection and bleeding. Management of AA is a difficult problem involving symptomatic treatment with transfusion of blood elements and antibiotic administration, both of which are very costly. Specific treatment with anabolic steroids gives a low rate of response; only 20 per cent of patients so treated recover.[2] Fifty per cent of patients die within the first 3 months of the diagnosis, due to severe infections and bleeding. Since response to anabolic steroids takes at least 3 months, severe cases are unlikely to survive long enough to benefit from therapy. Bone marrow transplantation has been shown to be an effective therapy in patients with severe AA and it gives better survival than for patients treated with anabolic steroids.[3] However, this procedure is very expensive and not available world-wide and only 30-40 per cent of patients can find HLA-compatible donors. Therefore, new modes of more widely applicable therapy are needed.

Over the past decade, there has been clinical and laboratory evidence suggesting that AA arises in some cases due to an autoimmune mechanism and interest has focused on the possibility of treating patients by immunosuppressive therapy.[4] The use of immunosuppressive agents such as cyclophosphamide in the treatment of AA is limited since such agents cause severe marrow suppression.[5] Subsequent studies have shown a significant increase in haematologic recovery and survival among patients receiving antithymocyte globulin (ATG) alone or ATG plus marrow infusion and anabolic steroids.[6,7] Again ATG therapy is expensive and associated with complications such as fever, chills, skin rash, hypotension and serum sickness. In a small group from Italy, high dose methylprednisolone was used instead of ATG and a therapeutic benefit was reported.[8,9] We thus evaluated the response to methylprednisolone treatment in 20 patients with AA.

PATIENTS

Twenty patients with AA were treated with methylprednisolone. The ages ranged from 13-67 years (median 27 years). Seven were female and 13 were male. Criteria for diagnosis of AA included haemoglobin less than 10 g/dl, white count less than $4 \times 10^9/1$, platelets less than $100 \times 10^9/1$ and hypocellular (less than 25 per cent) or acellular bone-marrow. Clinical and haematologic data are summaried in

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Table 1 Clinical and haematologic data of 20 patients with aplastic anaemia

Case	Age	Sex	Etiology	Time from onset (months)	Prior treatment	Initial blood counts				Outcome
						Hb (g/dl)	WBC ($\times 10^9$/l)	Neutrophils ($\times 10^9$/l)	Platelets ($\times 10^9$/l)	
1	20	M	Unkown	17	Methyltestosterone	3.1	2.5	0.6	10	Good response: Hb 7.7, WBC 2.3×10^9, platelet 20×10^9 within 3 months and Hb 11.6, WBC 4.7×10^9, platelet 100×10^9 within 11 months after treatment
2	31	M	Drug	19	Methyltestosterone, Oxymetholone	1.5	3.4	1.3	0	No response
3	45	M	Drug	90	Methyltestosterone, Oxymetholone	4.2	2.3	1.1	0	No response
4	13	M	Unknown	29	Methyltestosterone	8.0	5.7	1.4	0	No response
5	18	M	Unknown	104	Methyltestosterone	3.0	2.0	0.6	5	No response, died of intracerebral haemorrhage 8 months later
6	66	F	Drug	14	Methyltestosterone	2.9	3.0	1.1	0	Good response: Hb 6.9, WBC 3.9×10^9, platelet 30×10^9 within 3 months and Hb 12.0, WBC 2.7×10^9, platelet 100×10^9 within 7 months after treatment
7	25	M	Unknown	30	Methyltestosterone, Methenolone, Fluoxymesterone	6.0	3.0	0.6	0	No response
8	24	M	Unknown	6	No	4.7	3.2	1.2	15	No response
9	63	F	Unknown	1	No	5.6	2.4	1.0	0	No response
10	29	F	Unknown	3	No	6.9	3.7	0.4	5	No response
11	33	M	Drug	1	No	4.9	2.5	1.5	10	Good response: Hb 12.2, WBC 3.3×10^9, platelet 20×10^9 within 3 months and Hb 13.4, WBC 4.7, platelet 25×10^9 within 11 months after treatment
12	41	M	Drug	1	No	5.0	1.7	0.4	0	No response
13	19	M	Drug	2	No	3.9	3.1	1.4	5	No response
14	19	M	Drug	8	No	6.4	1.2	0.7	0	No response, died of septicaemia 3 months later
15	21	F	Unknown	2	No	4.4	3.8	1.7	0	No response
16	21	F	Unknown	9	No	5.8	2.3	1.2	15	No response
17	13	M	Unknown	4	No	4.5	4.6	1.0	0	Good response: Hb 11.2, WBC 5.1×10^9, platelet 20×10^9 within 6 months after treatment
18	67	F	Unknown	1	No	9.7	4.1	0.9	10	No response
19	34	M	Unknown	8	No	4.6	2.1	0.9	0	No response
20	32	F	Drug	1	No	6.4	2.4	0.9	0	Good response: Hb 10.9, WBC 4.2×10^9, platelet 10×10^9 within 3 months and Hb 10.7, WBC 7.8×10^9, platelet 10×10^9 within 6 months after treatment

Table 1. Eight patients had a history of drug exposure whereas the cause of AA was unknown in the remaining 12 cases. The interval from diagnosis to the start of methylprednisolone therapy was 14-104 months in 7 cases (no. 1-7) and 1-9 months in 13 cases (no. 8-20). Seven cases (no. 1-7) had received uneffective anabolic steroid treatment prior to methylprednisolone treatment.

Methylprednisolone was administered intravenously at a dose of 1 g daily for 3 days. Methyltestosterone 75 mg daily was added for patients who had never received anabolic steroids (no. 8-20). Packed red cells were transfused when symptoms of anaemia developed and platelets were transfused into patients who had bleeding. Infections were treated as appropriate. The duration of follow up varied from 3-24 months.

Only patients who had evidence of haematologic improvement within 3 months after therapy were considered to have responded to treatment. The degree of response was defined by the subsequent sustained level of improvement as follows: (1) complete response : return of a normal haemoglobin, white count of more than $4 \times 10^9/1$ and platelet count of more than $100 \times 10^9/1$; (2) partial response : improvement in all three cell lines but not reaching the levels defined as a complete response; and (3) no response : patients remaining pancytopaenic at 3 months or dead.

RESULTS

Five out of the 20 patients (25 per cent) improved within 3 months after methylprednisolone therapy. Two patients died (no. 5, 14), one due to intracerebral haemorrhage and the other due to septicaemia. Thirteen patients survived but did not improve. Response to methylprednisolone in 5 patients was only partial. The initial signs of improvement consisted of stabilisation of the haemoglobin level, a decreased requirement for blood transfusions and a marked diminution in bleeding. Two cases (no. 11, 20) had haemoglobin levels above 10 g/dl; only one case (no. 20) had a white count more than $4 \times 10^9/1$ and none had a normal platelet count. Neither infection nor bleeding occurred among the patients who showed increased haemoglobin levels but they still had leucopaenia and thrombocytopaenia. A long term follow-up showed that haemoglobin was above 10 g/dl within 6-11 months after treatment in all cases; the white count was normal in 4 cases (no. 1, 11, 17 and 20) and the platelets were normal in only 2 cases (no. 1, 6). No serious side effects of methylprednisolone were observed in this study.

Table 2 summarises the characteristics of the patients studied, as divided into 2 groups. Group 1 : chronic cases which were refractory to anabolic steroids and had been diagnosed and observed in very long follow-up periods of 14-104 months prior to methylprednisolone therapy. Group 2 : new cases who had never received any treatment. Response to methylprednisolone was found in two out of the 7 chronic cases (28.5 per cent) and in 3 out of the 13 new cases (23 per cent). The two responders of group 1 had developed AA relatively soon before the beginning of methylprednisolone therapy.

Table 2 Characteristics of patients as divided into chronic and new cases

	Chronic cases	New cases
Number of patients	7	13
Median age (range) (yr)	25 (13-66)	29 (13-67)
Male : Female	6:1	7:6
Median interval from onset of disease to methylprednisolone treatment (range) (months)	29 (14-104)	2 (1-9)
Cause of AA (no. of patients)		
Unknown	4	8
Drug	3	5
Prior treatment		
Anabolic steroids	7	0
Response to methylprednisolone (%)	2 (28.5)	3 (23.0)

DISCUSSION

Bacigalupo *et al* treated AA patients with methylprednisolone according to a following schedule: 20 mg/kg/d intravenously on the first 3 days; 10 mg/kg/d on days 4-7; 5 mg/kg/d on days 8-11; 2 mg/kg/d on days 12-20 and 1 mg/kg/d until day 30.[8,9] Three out of 6 patients (50 per cent) achieved a complete remission with full haematologic reconstitution.[8] We used this regimen to treat some patients but all of them died of infectious complications (unpublished observations). In order to avoid these serious complications, we used a short-term high dose methylprednisolone therapy

Response to methylprednisolone in this series was found in 5 out of 20

patients (25 per cent). Three out of 13 new AA cases and 2 out of 7 chronic cases recovered as a result of the treatment. No serious complications were observed. Subsequent studies by Bacigalupo *et al* found that only 5 out of 20 new cases (25 per cent) responded to long-term high dose methylprednisolone treatment.[9] With long-term high dose methylprednisolone, Sanz *et al* found 4 responders out of 5 patients who had been refractory to several previous treatments.[10] However, only 2 patients had complete remission; the others had relapse after cessation of treatment. Response to methylprednisolone in this series is not superior to anabolic steroid treatment in historical controls.[2,11]

The efficacy of therapy in patients with AA has always been difficult to assess. Haematologic recovery in these patients might be a result of spontaneous remission as shown in previous studies.[12,13] This phenomenon may occur more commonly than is generally appreciated. Also the responders in the first group (new cases) received methylprednisolone in combination with methyltestosterone and haematologic recovery in these cases might have resulted from the anabolic steroids. However, patients in the second group (chronic cases) received only methylprednisolone, since methyltestosterone had been discontinued for more than 3 months before. Haematologic response in these patients was therefore less likely to be due to anabolic steroids.

Possible explanations for the low response of methylprednisolone in this series include (1) insufficient methylprednisolone used; (2) methylprednisolone may be an inappropriate immunosuppressive agent for the treatment of AA; and (3) response is found only in AA patients whose bone marrow failure is immunologically mediated.

Our studies on the pathogenesis of AA in Thailand using *in vitro* progenitor cell cultures show that only a few patients have immune mediated bone marrow failure (unpublished observations). Based on these data, only a small population of AA will benefit from immunosuppressive therapy. However, a clinical trial is being launched with more effective immunosuppressive agents such as antithymocyte globulin. A modified regimen of short-term high dose methylprednisolone followed by alternate day high dose prednisolone is also being investigated. The results will be correlated with *in vitro* studies. Any recommendations for AA therapy will be based on the results of these studies.

ACKNOWLEDGEMENTS

We would like to thank Upjohn Company, Kalamazoo, MI, U.S.A. for supplying methylprednisolone. This work was supported by the Wellcome Trust and Mahidol University Research Grants.

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