

# Improvement of Platelet Counts in Steroid-Unresponsive Idiopathic Immune Thrombocytopenic Purpura After Short-Course Therapy With Recombinant $\alpha$ 2b Interferon

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In 13 patients with severe steroid-refractory idiopathic immune thrombocytopenia (ITP), a short course of recombinant  $\alpha$  2b interferon (IFN), given at a dose of 3 MU for 12 doses, caused a significant increase in platelet count in 11 patients. The rise in platelet count occurred following completion of the short course of IFN in 10 patients and occurred during therapy in one patient. Three patients showed an increase to normal platelet counts within 14 days of discontinuing the drug, eight showed a partial response, with a platelet count increase from 30 to 100  $\times$

$10^9/L$ , and two patients showed minimal response. One complete responder relapsed at 5 months from initial response, and a further course of  $\alpha$  2b IFN caused a second prompt response with a rise of platelet count to supranormal levels. Short-course  $\alpha$  2b IFN can be recommended as a therapy for severe ITP. Responses are seen in splenectomized and nonsplenectomized subjects, and thrombocytopenia is not exacerbated during treatment.

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**R**ARELY, immune thrombocytopenic purpura (ITP) can pose overwhelming clinical problems if conventional therapy such as steroids, splenectomy, and intravenous (IV) gammaglobulin therapy have failed. In one such case, life-threatening bleeding compelled us to try  $\alpha$  2b interferon (IFN) on the basis that it might modify B-cell activity involved in autoantibody production. Previous chlorambucil therapy in this patient, aimed at reducing putative B-cell clones, produced a transient improvement, and  $\alpha$  2b IFN was considered to be a nontoxic alternative to this alkylating agent (Fig 1). This therapy in the first patient did not produce an improvement in platelet count after 12 injections and, because of a decrease in granulocyte count, IFN was stopped. Following cessation of therapy, there was an exponential increase in platelet count over the next 7 to 14 days, which was sustained for 5 months without further therapy. Two subsequent patients who had refused splenectomy were treated with 12 doses of  $\alpha$  2b IFN  $3 \times 10^6$  U and showed an identical response.<sup>1</sup> Since then, 10 more patients were studied to assess which groups of ITP patients would benefit from therapy and to assess toxicity and the duration and extent of responses. This report provides preliminary information on these aspects of this novel approach to therapy in steroid-resistant ITP.

## MATERIALS AND METHODS

Thirteen patients with documented severe steroid-nonresponsive ITP have been treated on the IFN schedule, and the details of previous therapy for ITP and basic hematologic parameters are

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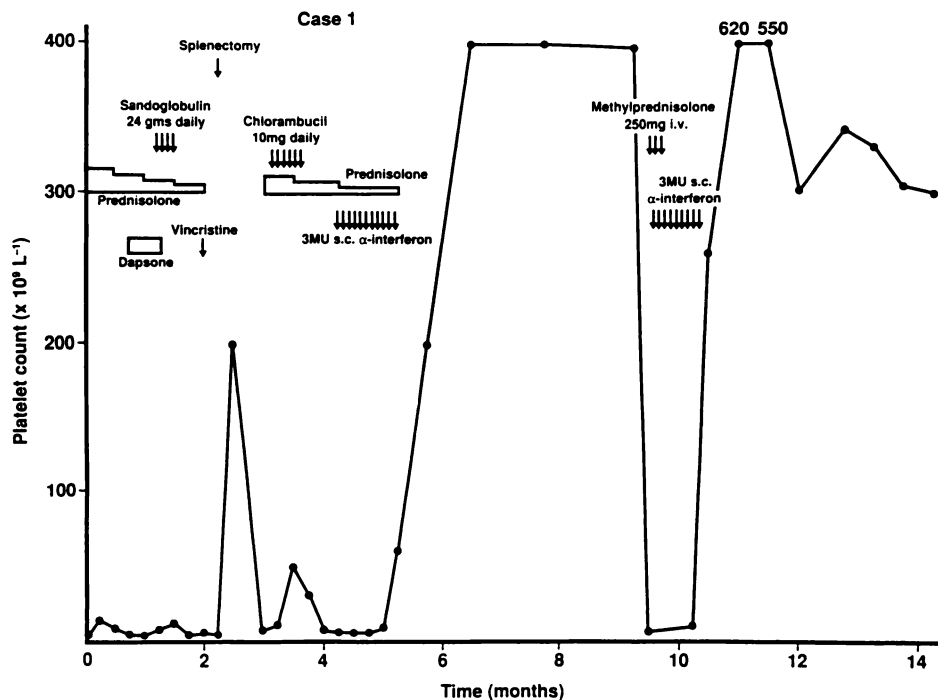
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shown in Table 1. All patients had documented ITP of various durations and had bone marrow appearances demonstrating normal erythropoiesis and myelopoiesis. In all cases there was an increase in number of megakaryocytes in bone marrow. Platelet-associated IgG (PaIgG) was estimated in 13 patients using the radio-labeled staphylococcal protein A method of Shaw et al.<sup>2</sup> The results are expressed as a binding ratio of binding to ITP platelets versus pooled normal control platelets. The normal range of PaIgG ratio for a cohort of 50 normal people was less than 1.65 (mean,  $0.89 \pm 2$  SD). Of the 13 patients, eight had increased amounts of PaIgG before treatment with IFN (Table 1). Immediately following IFN therapy, PaIgG levels were remeasured in eight patients; overall, no significant changes in levels had occurred. In Patient 3, an apparent marked increase in PaIgG was noted after treatment with IFN (Table 1).

None of the patients had concurrent or recent clinical viral infections and, in particular, none had clinical or serologic evidence of HIV or hepatitis B infection. All fulfilled the criteria for a diagnosis of ITP. The therapy protocol called for the administration of 12 injections of  $3 \times 10^6$  U  $\alpha$  2b IFN (Schering, Kenilworth, NJ) subcutaneously. Three injections were administered per week. Those patients who were normally on steroid maintenance were continued on the same dose throughout the study (Table 1), and no additional therapy was administered, other than blood products according to clinical need.

## RESULTS

In all patients the IFN therapy was well-tolerated, and compliance with the schedule was complete, with the exception of Patient 1, who received slightly shortened courses (Table 1). During therapy there was no fall in platelet count in any case, and there was a clinical impression of improvement of bleeding diathesis during therapy. In only one patient did the platelet count actually rise substantially while IFN was administered. In this case, the platelet count fell again after discontinuation of IFN. Figure 2 demonstrates the degree of elevation of the platelet counts during and following the use of IFN and shows that the initial three patients treated had a platelet count increase to normal, which was sustained for several months. Details of patient 1, who has now been treated on two occasions with IFN following relapse, are shown in Figure 1. Other patients had a partial response to IFN of shorter duration, and two patients showed minimal response at this dosage of IFN. There was no difference in response between patients who had had previous splenectomy and nonsplenectomized



**Fig 1. Details on patient 1.** The patient was steroid-insensitive from the outset, and IV gammaglobulin was ineffective. IFN was tried after partial response to chlorambucil, as it was felt that IFN might mimic chlorambucil response. A second course of IFN was effective 5 months later. The courses of IFN were slightly curtailed because of a decrease in granulocyte count.

patients. The PalgG level, when available, did not demonstrate any change from the pretreatment levels at the end of the IFN course or 1 month after completion of the IFN in the three complete responders. This suggests that the mechanism is possibly independent of antibody production or that the test used is insufficiently sensitive to pick up detailed changes.

Of particular importance is patient 1 (Fig 1), who had been off treatment for 5 months following the first IFN course and then demonstrated an acute relapse of the condition, with severe generalized bleeding. At the acute onset of bleeding, three injections of methylprednisolone 250 mg were given over 24 hours, following which no increase in platelets occurred. This was followed by a further nine injections of IFN ( $3 \times 10^6$  U) over 4 weeks. Once again, there was no increase in platelet count during therapy, but 3 days after discontinuing the second course, the platelet count once again increased, and within 21 days had reached a further peak level of  $630 \times 10^9/L$ . It must be noted that this patient was initially totally steroid-unresponsive. Whether the IFN and steroid treatment were synergistic in this patient's second treatment remains uncertain.

Four patients in Fig 2 who demonstrated a partial response on IFN had a similar partial response on subsequent reintroduction of IFN at the same dose. Four other patients with a partial response have not required retreatment. In one of the nonresponders, an additional prolonged course of IFN using 3 MU daily for 6 weeks did not cause any decrease in platelet count, nor was there any rebound increase on stopping IFN.

It is important to note that in the patients demonstrating a complete response, a significant decrease in the absolute granulocyte count occurred over the IFN treatment period (Table 1). This had been the reason for stopping treatment

early in Patient 1. We also noted that in those patients who demonstrated only partial or no response, the granulocyte count decrease was less marked or absent. It may subsequently be possible to use the granulocyte count to indicate the dose or duration of IFN treatment in an individual patient.

#### DISCUSSION

We have demonstrated that short-course, low-dose  $\alpha$  2b IFN is of undoubted clinical benefit in some cases of severe steroid-nonresponsive ITP. This therapy is inexpensive, well-tolerated, and the experience in one of our patients suggests that complete responses can be seen in subsequent relapses. The initial experience of using such a short course was a chance finding because of relative granulocytopenia occurring in the first patient necessitating stopping the course of treatment early. The characteristic response of the platelet count is for the substantial rise to occur after the IFN has been discontinued. Our impression of the patients treated so far is that the patients in whom a marked granulocyte count decrease occurs during treatment are those who subsequently appear to have a rebound increase in platelet count. IFN has been noted to be of value in the thrombocytopenia associated with HIV-positive patients, and in these case studies,<sup>3,4</sup> IFN was continued for several months and platelet counts increased while the patients continued on the drug. It would appear from our study that such prolonged treatment is not always necessary in ITP, though in the patients who did not respond to short-course treatment, alternative dose schedules should be evaluated further.

Previous information relating to  $\alpha$  2b IFN and platelets has concentrated on its use in lowering platelet counts to treat thrombocytopenia and myeloproliferative disorders.<sup>5</sup> It

Table 1. Previous Therapy for ITP and Basic Hematologic Parameters

Patient No.	Sex/Age	Pre-Rx PalgG Ratio to Normal	Post-IFN PalgG Levels	Previous Treatment	Prior Splenectomy
1a	F/37	+ve 3.0	+ve 3.0	Steroids Gammaglobulin Dapsone	Yes
1b	F/37	+ve 3.0	+ve 1.8	Vincristine Chlorambucil	Yes
2	F/70	-ve 1.0	-ve 1.0	Steroids	No
3	F/65	+ve 2.8	+ve 16.7	Steroids Vincristine Danazol Chlorambucil	No
4a	F/18	+ve 6.0	+ve 6.0	Steroids	No
4b	F/18	+ve 6.0	NA	Steroids	No
5	M/40	-ve 1.5	-ve 1.5	Steroids	Yes
6	M/56	+ve 6.3	NA	Steroids Gammaglobulin Azathioprine	Yes
7	F/59	+ve 2.2	NA	Steroids Gammaglobulin	Yes
8	F/61	+ve 2.2	NA	Steroids	Yes
9	F/41	+ve 1.9	NA	Steroids	Yes
10	F/58	-ve 1.0	-ve 1.0	Steroids	No
11	M/57	-ve 1.5	-ve 1.5	Steroids	Yes
12	F/61	-ve 1.5	-ve 1.5	Steroids Gammaglobulin	Yes
13	F/27	+ve 2.3	+ve 2.3	Steroids	No

Patient No.	Platelet Count		Steroid Treatment During IFN	Time to Maximum Response (d)	Neutrophils $\times 10^9/L$		Total No. of IFN Doses ( $3 \times 10^6$ )	Duration of Responses (wk)
	Pre-IFN	Maximum Post-IFN			Pre-IFN	Post-IFN		
1a	6	491	Yes	24	3.2	0.98	11	26
			Reducing dose					
1b	5	730	No	46	3.2	1.5	9	28
2	20	202	No	35	12.2	3.0	12	36
3	2	527	Yes 20 mg	31	8.3	2.8	12	55+
4a	15	57	No	21	4.1	2.1	9	4
4b	14	45	No	23	2.8	1.1	12	3
5	5	9	No	NA	6.5	5.0	12	NA
6	23	56	No	63	2.6	2.3	12	36+
7	18	50	No	35	13.2	12.5	12	5+
8	10	19	Yes 20 mg	NA	2.9	3.2	12	NA
9	7	154	No	37	NA	NA	12	8
10	14	243	No	10	NA	NA	12	4+
11	14	99	No	64	4.6	2.8	12	15+
12	21	57	No	63	3.23	4.6	12	25+
13	16	111	No	38	10.0	4.56	12	14+

Response to interferon occurs in patients whether or not they have had previous splenectomy. Note that the fall in absolute granulocyte count occurred to a greater extent in patients demonstrating complete response.

Abbreviations: NA, data not available; -ve, negative; +ve, positive.

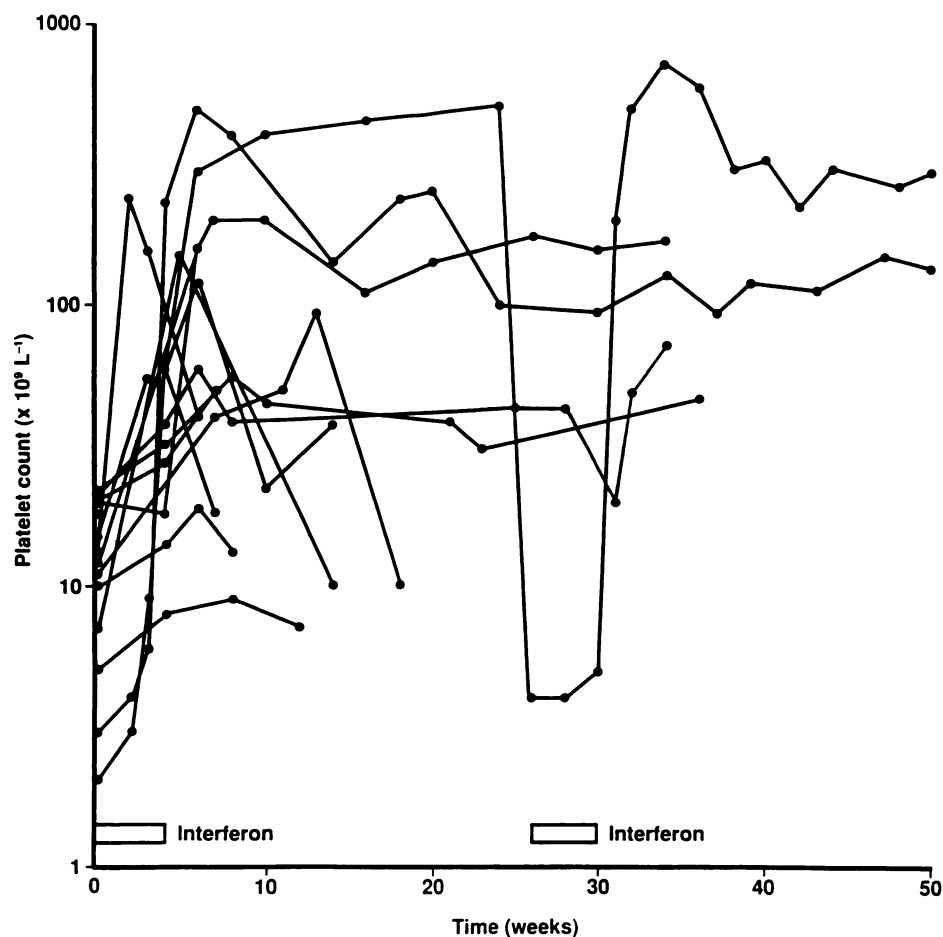


Fig 2. Overall pattern of platelet response in 13 patients. Four patients with partial response showed similar responses on a further course of treatment (data not shown). Four additional patients with partial response were not retreated. None of the patients demonstrated a fall in platelet count on therapy. The block of interferon at 30 weeks relates to use in patient 1 only (see Fig 1 for details).

is also known that  $\alpha$  2b IFN is associated usually with a fall of platelet count when used for treatment of hairy-cell leukemia.<sup>6</sup> There is, of course, an apparent paradox here that we cannot explain at present, as the mechanism of action of IFN in ITP has yet to be elucidated. It is tempting to speculate that in some way  $\alpha$  2b IFN modulates the cellular and humoral immunologic interactions that are known to be

disturbed in untreated ITP.<sup>7</sup> This will be an important area of investigation in subsequent studies.

We can safely recommend the use of this therapy in steroid-unresponsive patients with ITP. We consider that IFN will find a place in the treatment of idiopathic ITP, as in its recombinant form it does not carry the risk of any transmissible agents.

#### REFERENCES

1. Proctor SJ, Jackson G, Carey P, Stark A: Short course alpha interferon therapy in severe unresponsive immune thrombocytopenia. *Lancet* 1:947, 1988
2. Shaw GM, Axelson J, Maglott JG, Lobuglio AF: Quantification of platelet bound IgG by I<sup>125</sup> staphylococcal protein A in immune thrombocytopenia purpura and other thrombocytopenic disorders. *Blood* 63:154, 1984
3. Ellis ME, Neal KR, Leen CLS: Alpha-2a recombinant interferon in HIV associated thrombocytopenia. *Br Med J* 295:1519, 1987
4. Lever AML, Brook MG, Yap I, Thomas HC: Treatment of thrombocytopenia with alpha interferon. *Br Med J* 295:1519, 1987
5. Giles FJ, Gray AG, Brozovic M, Grant IR, Machin SJ, Richards JDM, Venutas S, Singer CRJ, Young KL, Davies SC, Hoffbrand AV, Mehta AB, Thomas MJG, Goldstone AH: Alpha-interferon therapy for essential thrombocythaemia. *Lancet* 2:70, 1988
6. Worman CP, Catovsky D, Bevan PC, Camba L, Joyner M, Green PJ, Williams HJH, Bottomley JM, Gordon-Smith EC, Cawley JC: Interferon is effective in hairy-cell leukaemia. *Br J Haem* 60:759, 1985
7. Mylvaganam R, Garcia RO, Ahn YS, Sprinz PG, Kim CI, Harrington WJ: Depressed functional and phenotypic properties of T but not B lymphocytes in idiopathic thrombocytopenic purpura. *Blood* 71:1455, 1988