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Human Leucocyte Interferon-α Therapy can Induce a Second Response in Treatment of Thrombocytosis in Patients With Neutralising Antibodies to Recombinant Interferon-α2a

M. Merup, E. Törnebohm-Roche, K. Engman and C. Paul

INTERFERON-α (IFN-α) can effectively normalise thrombocytosis in polycythaemia vera (PCV) and essential thrombocythaemia (ET) [1]. IFN-α is an endogenous subtance with no leukaemogenic potential. It is an attractive therapy for younger patients since treatment with radioactive phosphorus and alkylating agents results in a highly increased incidence of acute leukaemia [2, 3].

Natural antibodies to IFN-α appear spontaneously without exogenous administration of IFN-α [4], but the most common trigger for formation of antibodies to IFN-α is treatment with exogenous IFN-α. Development of neutralising antibodies seems to be more common during treatment with recombinant IFN-α2a (rIFN-α2a) where frequencies between 20 and 29% have been reported [5, 6].

Interferon Alfanative® is a highly purified preparation of human leucocyte IFN-α that contains approximately 20 different IFN-α subtypes. During treatment with this drug no development of neutralising antibodies has been described [7].

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This is a report of 2 patients with PCV and ET complicated with elevated platelet counts who developed neutralising antibodies during treatment with IFN-α2a. After change of therapy to human leucocyte IFN-α, a second response to therapy could be achieved.

Case 1

A 68-year-old, previously healthy woman was admitted in December 1990 because of vertigo and vision disturbances. At diagnosis, a haematological analysis showed haemoglobin 200 g/l, erythrocyte volume fraction 66%, leucocyte count (LPK) 13.6 × 10^9/l, and a platelet count of 588 × 10^9/l. The blood volume was increased by 25%. A bone marrow aspiration

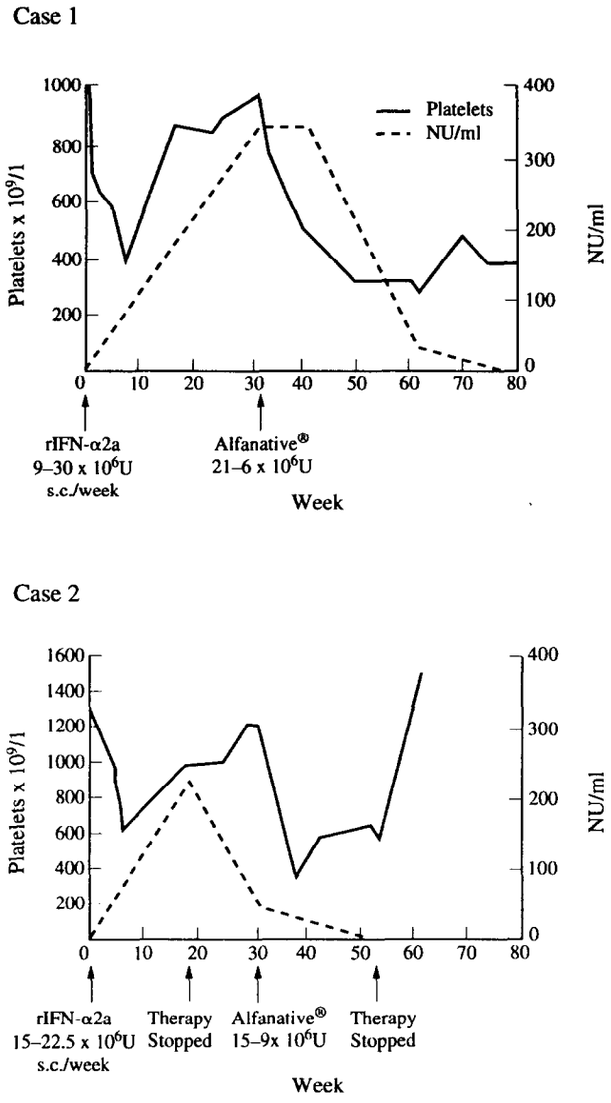

Figure 1. Platelet levels and titres of neutralising antibodies to rIFN-α2a in 2 patients with elevated platelets due to essential thrombocythaemia and polycythaemia vera. After initial response and subsequent treatment failure on rIFN-α2a, a second response was achieved after changing to human leucocyte IFN-α (Alfanative®). In case 2, treatment had to be discontinued due to induction of rheumatoid arthritis. The dotted line indicates neturalising antibodies to rIFN-α2a in neutralising units per ml.

was compatible with the diagnosis of PCV. Therapy with phlebotomies was started concomitant with low-dose aspirin. During the first 4 months of treatment, eight phlebotomies of 400 ml blood were needed in order to keep the erythrocyte volume fraction below 45%. Because of episodes of vertigo and increasing platelets (997×10^9/l), treatment with rIFN-α2a (Roceron-A) was started in April 1991. Before response to therapy, the patient suffered from several transient cerebral ischaemic attacks. After 7 weeks of treatment, the platelet count was 406×10^9/l, haemoglobin was 123 g/l and LPK was 6.3×10^9/l. In August, a sudden rise in the platelet count to 871×10^9/l and LPK to 16.9×10^9/l was seen. Analysis showed a titre of 350 neutralising units (NU)/ml of antibodies to rIFN-α2a but no antibodies against human leucocyte IFN-α.

In December, the platelet count was 986×10^9/l. LPK was 19.8×10^9/l and haemoglobin 140 g/l, and treatment with Interferon Alfanative® 3 million U daily was started. After 15 weeks of treatment, platelet count was 334×10^9/l, LPK was 6.5×10^9/l and haemoglobin was 134 g/l. The number of weekly IFN injections was gradually reduced. After 22 months of treatment, currently with 3 million U twice weekly, the patient is still in complete remission. There has been no need for phlebotomies during the last 19 months.

Case 2

A 51-year-old woman with previous episodes of severe arthralgia in her fingers and feet, that had required treatment with NSAID drugs was admitted. From September 1991, she experienced increasing fatigue and vision disturbances. Haematological analysis showed haemoglobin 133 g/l, leucocyte count 12.5×10^9/l, platlet count 1300×10^9/l, and a sedimentation rate of 5 mm. The bone marrow was hypercellular and LAP score was increased to 157. The diagnosis of ET was made. Analysis showed no antibodies to IFN-α. Treatment with rIFN-α2a (Roceron-A®) was started in February 1992, and platelets declined to 621×10^9/l and LPK to 9.0×10^9/l after 6 weeks. During treatment, the patient experienced severe arthralgia and was referred to a rheumatologist. She was found to have a seropositive rheumatoid arthritis. Platelets started to rise and analysis of IFN antibodies showed neutralising antibodies against rIFN-α2a with a titre of 220 NU/ml, but no neutralising antibodies against human leucocyte IFN-α. Treatment with rIFN-α2a was discontinued. In September 1992, the platelet count was 1208×10^9/l, haemoglobin 124 g/l and LPK 14.4×10^9/l, and treatment with interferon Alfanative® 3 million U five times per week was initiated. After 7 weeks of treatment, platelets were 364×10^9/l and LPK 5.0×10^9/l, and injections were reduced to 3 million U three times per week. At this point, platelets increased to 574×10^9/l and treatment was intensified. The patient experienced severely intensified pain in her fingers, shoulders and elbows and transient swelling of joints was noted. Sedimentation rate increased to 56 mm, compatible with an increased activity of the rheumatoid arthritis. In February, the patient was further disabled with arthritic pain and could not continue working. The platelet level was 556×10^9/l. Since a negative effect on the arthritic pain from IFN treatment could not be excluded the therapy was discontinued in February. However, joint symptoms gradually increased, and in April the patient was taken into hospital for intensified treatment of her rheumatoid arthritis. She was then found to have arthritis in fingers, elbows and feet and medication with methotrexate was initiated. At this point the platelet level had increased to 1500×10^9/l.

DISCUSSION

This is a report of two cases where a second response to therapy was induced with human leucocyte IFN-α after treatment failure with rIFN-α2a. Antibodies also neutralised rIFN-α2b *in vitro*, although none of the patients had been treated with this type of IFN previously. *In vitro*, there was no neutralising action to natural leucocyte IFN-α. After switching to human leucocyte IFN-α, the titres of neutralising antibodies gradually disappeared in both patients.

One patient has remained on therapy for more than 22 months with normal platelet and leucocyte counts, and it has been possible to reduce the dose of IFN gradually to the present maintenance dose of 6 million U/week. Before IFN treatment, phlebotomies were performed eight times in 4 months, and during the next 11 months, five more phlebotomies were performed. After normalisation of thrombocytosis, no more phlebotomies have been necessary. There has been no episodes of bleeding or major thrombocmbolic events.

In addition, the second patient had a dramatic second response to therapy, which normalised her platelet count. Treatment was complicated by activation of a seropositive rheumatic disease. After withdrawal of interferon medication, the rheumatic disease has remained active for more than 6 months, but the activity has gradually decreased on methotrexate treatment. Platelets have rapidly risen to pretreatment levels.

There are several reports of development of autoimmune antibodies and induction of autoimmune disorders after therapy with α-interferon, and cases of a symmetric inflammatory arthritis resembling rheumatoid arthritis have been reported to arise during IFN-α treatment [8, 9]. The patient in the present report had previously experienced an episode of severe arthritic pain. During the first treatment with rIFN-α, symptoms reoccurred and the seropositive rheumatic disease was then first diagnosed. During the longer treatment period with human leucocyte IFN, the symptoms were further augmented. Thus, the rheumatic disease may have been activated by treatment with IFN-α.

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