

AUTOIMMUNE HEMOLYTIC ANEMIA DURING ALPHA INTERFERON TREATMENT IN NINE PATIENTS WITH HEMATOLOGICAL DISEASES

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ABSTRACT

Background. A number of side effects have been observed in patients treated for hematological diseases with α -interferon (IFN). In several cases side effects consisted of immunological disorders. Autoimmune hemolytic anemia (AIHA) is the most typical example of an IFN-induced immune-mediated complication.

Case series. In 10 years we observed 9 patients with various hematological disorders who developed AIHA during IFN treatment. The interval between the start of IFN treatment and the onset of acute hemolysis suggests a dual pattern of occurrence: (1) early onset (interval 1 to 21 days), seen in patients who had anti-RBC antibodies before IFN treatment; (2) late onset (interval 3-38 months), in patients with no history of anti-RBC antibodies at the start of treatment. Discontinuation of IFN, often associated with prednisone treatment, caused prompt hematological recovery in all cases; anti-erythrocyte antibodies persisted in the first group of patients and disappeared in the second.

Conclusions. In rare cases IFN may cause AIHA. The immunological derangement caused by IFN seems to act at two different levels: enhanced destruction of antibody-coated RBCs and induction of autoreactive B-cells. As for the possibility of other preexisting immunological disorders, AIHA (even latent) is a contraindication to IFN treatment. Patients treated with IFN need accurate monitoring to guard against for the development of autoimmune disorders.

Key words: interferon- α , autoimmune disorders, autoimmune hemolytic anemia

Interferons (IFN) have been used over the past 15 years for the treatment of infectious, hepatic, hematological and oncological diseases. In hematology, (α -IFN has been used to treat hairy cell leukemia, chronic myeloid leukemia, other chronic myeloproliferative diseases, low-grade non-Hodgkin's lymphoma, multiple myeloma, cryoglobulinemia, and Waldenström's macroglobulinemia. Due to the large number of patients enrolled in multicentric studies, numerous reports of side effects

have appeared. These can be grouped into two main categories: (a) non immunemediated; (b) probably or certainly immunemediated. The first group includes a flu-like syndrome, leukopenia, toxicity to digestive, cardiovascular and central nervous systems, pancreatitis.¹ The second group includes skin rash, alopecia, acute renal failure or nephrotic syndrome, regional lymphadenopathy after intralesional use, endocrinopathies, collagenopathies, sarcoidosis, myasthenia gravis, pernicious anemia,

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Note: this Short Report is signed by 8 authors as an exception to the rule that these small articles should have no more than 6 authors. This exception is justified by the multicenter nature of this report.

Received January 15, 1996; accepted April 10, 1996.

hemolytic uremic syndrome, hemolytic anemia, thrombocytopenia and worsening of post-transplant graft-versus-host disease.²⁻⁷ We report here on 9 patients who developed Coombs'-positive autoimmune hemolytic anemia (AIHA) during IFN treatment for a hematological disorder. The dual pattern of onset and remission suggests that IFN affects the immune response at multiple levels, causing both exacerbation of preexisting and appearance of *de novo* autoimmune disorders.

Case series

From 1985 to 1995 we collected from five institutions 9 cases of acute AIHA in patients treated for a hematological disorder with IFN. Table 1 summarizes the most relevant clinical data. Except for 2 patients with CML, all of them had been receiving IFN for a lymphoproliferative disorder, usually as participants in clinical trials. The majority of these patients were receiving small doses of IFN (9 International Mega Units per week), except for the two patients with CML who were getting 27 IMU per week. A direct antiglobulin test (DAT) for anti-RBC antibodies was known to be positive before IFN treatment in 4 patients without clinical signs of hyperhemolysis at the start of IFN treatment; no information on the DAT test before IFN treatment was available for the other 5 patients, but none of them had a history of

hemolytic anemia. In all cases hyperhemolysis was acute and severe and was associated with a positive DAT test. The anti-RBC antibodies were characterized in 5 patients and found to be panagglutinant in all cases; Ig class was IgG in 4 cases and IgA in one. The interval between the start of IFN and the occurrence of acute hemolysis varied from 1 day to 38 months; 4 patients developed acute anemia after 1 to 21 days, 5 patients after 3 to 38 months, no patient between 1 and 3 months. Thus, although the series is small, a bimodal pattern could be suspected. Indeed the two groups of patients differed in one important feature: the DAT test was known to be positive before the start of IFN in all patients with early onset of acute hemolysis. IFN was immediately discontinued in all patients, and most of them received intermediate doses of prednisone (0.5-1 mg/kg) for 1 to 3 months. All patients recovered from hyperhemolysis; the DAT test remained positive in the patients who had been positive before IFN administration and became negative in a few months in the others.

Discussion

IFN treatment can exacerbate preexisting autoimmune disorders,⁸ causing either clinical worsening or reactivation of a latent disease; it may also induce *de novo* autoimmune disorders. The immunological derangement leading to

Table 1. Characteristics of the 9 patients with IFN-related AIHA.

Pt.#	sex	age	diagnosis	IFN type	IFN treatment duration	Hb nadir (g/dL)	DAT before IFN	DAT at hemolysis	DAT at recovery	AIHA treatment
1	F	71	HCL	α 2b	1 day	6.5	+	+	+	PDN
2	F	81	WM	α 2b	3 days	6.0	+	+	+	None
3	F	61	CLL	α 2b	7 days	5.8	+	+	+	PDN
4	F	57	NHL	α 2b	21 days	8.1	+	+	+	PDN
5	M	60	CLL	α 2b	3 mo.	7.3	na	+	-	PDN
6	F	55	WM	α 2b	4 mo.	7.2	na	+	-	PDN
7	M	75	MM	α 2b	5 mo.	4.3	na	+	-	PDN
8	F	59	CML	α 2b	27 mo.	7.7	na	+	-	PDN
9	F	59	CML	α 2a	38 mo.	7.0	na	+	-	PDN

na: not available; HCL: hairy cell leukemia; WM: Waldenström's macroglobulinemia; CLL: chronic lymphocytic leukemia; NHL: non-Hodgkin lymphoma; MM: multiple myeloma; CML: chronic myeloid leukemia. PDN: prednisone.

these complications is poorly understood. AIHA is an excellent model of an antibody-mediated autoimmune disorder because the clinical consequences are readily apparent and the specific antibody can be easily detected and monitored. In our series there were examples of both exacerbation and *de novo* appearance of AIHA. These two subgroups of patients differed in at least three features:

1) *timing*. The interval between the start of IFN and hemolytic crisis was quite different; preexisting latent hemolysis was exacerbated after a few days of IFN treatment, while *de novo* AIHA appeared after 3 to 27 months;

2) *primary disease*. While all patients in the first group (exacerbation) suffered from a lymphoproliferative disorder that could account for the preexisting latent hemolysis, the second group (*de novo* AIHA) included 2 cases of CML, a disease unlikely to be associated with immunological disorders;

3) *outcome*. Following discontinuation of IFN anti-RBC antibodies persisted in the first group (although without overt hemolysis) and disappeared in the second, suggesting that in the latter case IFN was required not only for the appearance but also for the maintenance of autoreactive B-cells.

Taken together, these findings suggest that multiple mechanisms are operating; exacerbation of latent hemolysis is most likely due to IFN-induced enhanced destruction of antibody-coated RBCs, while *de novo* AIHA comes from the expansion of IFN-induced autoreactive B-cells. Other biological modifiers such as growth factors, and lymphotoxic drugs such as fludarabine and 2-chlorodeoxyadenosine^{9,10} may cause AIHA through a complex immunological derangement that includes T-cell subpopulation imbalance, overexpression of class I histocompatibility antigens, NK-cell and/or macrophage activation, secretion of other cytokines.¹¹ IFN-induced autoimmune complications are infrequent. In a recent report on a large series of CML patients treated with α -IFN, autoimmune

complications occurred in 35 patients (5%) and AIHA in 7 (1%);¹² however, patients with lymphoproliferative disorders may have a higher propensity for developing immunological diseases. We suggest checking for immunological disorders in any patient undergoing IFN treatment, avoiding the use of IFN in the presence of an overt or latent immunological disease, and monitoring all patients on IFN treatment for the appearance of early or late onset immunological complications.

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