anti-interferon-α2a antibodies.[1] The authors conclude that "*using a non-cross-reactive type of IFN-α, such as a lymphoblastoid one, would not be advantageous in an attempt to recover a hematologic response*". Although we agree with the general meaning of this statement, our experience seems to indicate that treatment with IFN α-Ly can induce hematologic and cytogenetic responses in such patients, albeit this response is seen only in a minority of them. We speculated about the possibility of overcoming resistance directed at a definite subtype of IFN-α with the use of IFN-α-Ly, a mixture of many IFN-α components.[2] It has been shown that different subtypes of IFN-α display different antiproliferative activity against leukemic cell lines.[3]

Since 1991, ten patients have been treated with IFN-α-Ly (Wellferon®) after having an unsatisfactory response to rIFN-α2. The results on the first six patients have been communicated previously.[4,5]

Nine of our patients have been previously treated with r-IFN α2a, and one of them received r-IFNα2b. The treatment duration and results are depicted in Table 1. Hematologic and cytogenetic responses were classified according to Talpaz *et al*.[6] Two of the patients (# 1 and 6), with progressive disease after being treated with r-IFNα2, obtained a complete hematologic response after treatment with IFNα-N1. They also achieved a minimal genetic response (58% Ph1 and 80% Ph1). However, the genetic response was lost at the end of the follow-up. One patient (#6), whose last response to r-IFNα2 was minimal (94% Ph1 metaphases) after 3 years of treatment, achieved a major genetic response to IFN-α-Ly, with only 27% Ph1 positive metaphases. The time taken to obtain this response was 4 months. Conversely, IFN-α-Ly was not effective in the other seven patients. Toxicity was fairly similar to that of r-IFN-α2.

Table 1. Comparison of response between the different IFN preparations.

Pts	*Time of treatment with rIFNα2 (days)*	*Last HR to rIFNα2*	*Last GR to rIFNα2 (%Ph1)*	*Time of treatment with IFNαN1 (days)*	*HR to IFNαN1*	*GR to IFNαN1 (%Ph1)*
1	84	NHR	NE	868	CHR	mGR (58%)*
2	1006	CHR	NGR	209	CHR	NGR
3	160	PHR	NGR	377	PHR	NE
4	541	PHR	NGR	245	NHR	NE
5	1081	CHR	mGR (94%)	137	CHR	PGR (27%)°
6	101	NHR	NGR	441	PHR	mGR (80%)#
7	402	PHR	NGR	438	PHR	NGR
8	655	NHR	NGR	77	NHR	NE
9	184	NHR	NE	105	NHR	NE
10	244	NGR	NGR	144	NHR	NE

Legend. HR: hematologic response; GR: genetic response; CHR: complete hematologic response; PHR: partial hematologic response; NHR: no hematologic response; CGR: complete genetic response; PGR: partial genetic response; mGR: minimal genetic response; NGR: no genetic response; NE: not evaluated.
**Obtained at 313 days; °obtained at 137 days; #obtained at 146 days.*

Our results suggest that treatment with IFNα-Ly can give hematologic and cytogenetic responses in CML patients who have had a previous unsatisfactory response to rIFN-α2. However, some of these responses are transient, and major genetic responses are only achieved in a minority of them (one out of ten, in our series).

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References

1. Russo D, Candoni A, Grattoni, Minisinni R, Rosti G. Response to sequential treatment with lymphoblastoid interferon-α in patients with Ph+ chronic myeloid leukemia unresponsive to recombinant interferon-α (rIFNα2a) and neutralizing-rIFNα2a antibodies negative. Haematologica 1997; 82:348-50
2. Zoon KC, Miller D, Bekisz J, et al. Purification and characterization of multiple components of human lymphoblastoid interferon-α. J Biol Chem 1992; 267:15210-6.
3. Fish EN, Banerjee K, Stebbing N. Human leukocyte interferon subtypes have different antiproliferative and antiviral activities on human cells. Biochem Biophys Res Commun 1983; 112:537-5.
4. Steegmann JL, Peñarrubia MJ, Lavilla E, et al. Treatment with human lymphoblastoid interferon (IFNαN1) can rescue some chronic myeloid leukemia (CML) patients resistant to recombinant interferon α2 (r-IFNα2) and without anti-interferon antibodies. Br J Haematol 1994; 87:suppl 1:175.
5. Steegmann JL, Peñarrubia MJ, Fernandez-Ranada JM. Treatment with human lymphoblastoid interferon can rescue some chronic myeloid leukaemia patients resistant to recombinant interferon-α2 and without anti-interferon antibodies. The Royal Society of Medicine. London: Current Medical Literature, 1995. p. 207-4.
6. Talpaz M, Kantarjian HM, McCredie K, Trujillo JM, Keating MJ, Gutterman JU. Hematologic remission and cytogenetic improvement induced by recombinant human interferon-α in chronic myelogenous leukemia. N Engl J Med 1986; 314:1065-9.

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Cholestatic hepatitis secondary to the use of acenocoumarin

Sir,

As cholestatic hepatitis is a rarely reported untoward effect of dicoumarin compounds[1-3] with remarkable clinical and analytical consequences, we report herewith the following clinical observation.

A 90-year-old man previously diagnosed with atrial fibrillation was admitted to the hospital because of an arterial embolism in the inferior extremities. No other relevant pathological antecedents were present and with basic analytical profile was normal. He was treated by embolectomy followed by sodium heparin and acenocoumarin (Sintrom 10 mg/7 days). On successive follow-up, he presented occasional vomiting and the dose of dicoumarin therapy had to be progressively increased to 11, 14 and 16 mg/7 days, without reaching effective therapeutical levels. Concurrently, ALT, AST, AP and γGT

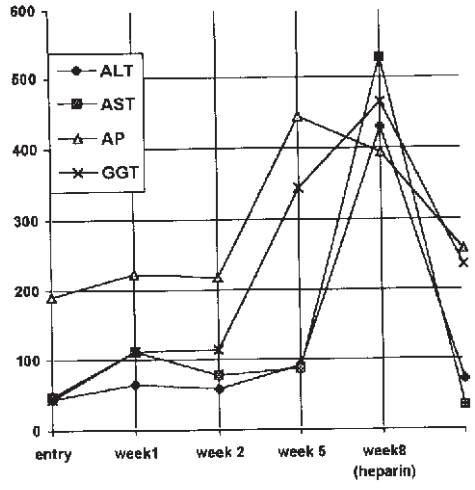

Figure 1. Enzymatic alteration in relation to time.

progressively increased (Figure 1) and the ecography was normal. Viral A, B and C HV markers were all negative. Liver biopsy was not considered because of the compromized hemostasis and the age of the patient. At 2 months, he was admitted because of another arterial embolism. Calcium heparin was initiated, while liver tests became progressively normal. On the seventh day, with defervescence in the thrombotic phenomena, he was released under calcium heparin, followed by low molecular heparin, which was sustained indefinitely, without recrudescence of the liver's enzymatic parameters.

The fast defervescence on the liver tests and the absence of other causative factors confirm the cause-effect relationship between the drug and the cholestasis, though we did not consider re-challenge for ethical reasons. Likewise, it is worth noting the low response to warfarin if we consider that recurrence was not avoided. This leads us to speculate that there is a metabolic resistance to the drug on a hepatic level, which would explain both phenomena observed in this patient. Although we have been able to find other reports about warfarin-related hepatitis,[4-6] we have not found similar complications after the treatment with acenocoumarin. We think that, in spite of the apparent scarcity of this drug-related hepatitis, this possibility should be taken into account because of the frequency of the anticoagulant treatment.

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References

1. Den Boer W, Loeliger EA. Phenprocoumon-induced jaundice. Lancet 1980; i:912.
2. De Man RA, Wilson JHP, Schalm SW, Ten Kate JW, Van Leer E. Phenprocoumon-induced hepatitis mimicking non-A non-B hepatitis. J Hepatol 1980; 11:318-21.
3. Kreiter H, Fink U. Ein Fall von Leberschändigung nach Cumarin-Medikation. Med Klin 1967; 62:12-5.
4. Rehnquist N. Intrahepatic Jaundice due to warfarin therapy. Acta Med Scand 1978; 204:335-6.
5. Höler T, Schnütgen M, Hemreich-Becker Y, Mayer zum Büschenfelde KH. Drug-induced hepatitis: a rare complication of oral anticoagulants. J Hepatol 1994; 21:447-9.
6. Chaundry S, Oelsner D. Cholestatic reaction to warfarin. Am J Gastroenterol 1995; 90:853.

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Thrombophilic condition in HIV-infected patients

Sir,

Various hemostatic disorders associated with hypercoagulable conditions have been reported in HIV infection, even in the absence of clinically apparent thrombosis and showing no correlation to the stage of the disease.[1,2] To further investigate whether HIV infection was associated with an ongoing prothrombotic state, twenty-two consecutive HIV-infected patients, classified as having AIDS (10 M, 12 F, aged 35±10; mean±SD), were studied during outpatient therapy for a certain length of time during acute episodes.

The control group consisted of twenty age- and sex-matched HIV-negative healthy individuals (9 M, 11 F, aged 30±4, mean±SD). None of the patients had laboratory or clinical evidence of hepatopathy or renal failure. None had a history of thrombosis or had received anticoagulant therapy. Since the analysis of the molecular markers of hemostatic parameters can lead to artefactually elevated results,[3] blood collection and handling were carried out under strictly standardized conditions. The activation of the coagulation system was studied measuring plasma concentrations of the prothrombin fragment 1+2 (F1+2) using ELISA (BeringWerke AG, Germany). The fibrinolytic system was investigated detecting plasma levels of plasminogen activator inhibitor (PAI-1) activity and fibrin degradation product (FbDP) with a chromogenic substrate-based assay and an immunoturbidimetric assay, respectively, according to manufacturer instructions (Boehringer Mannheim, Germany). Since infectious disease and sepsis, which are common occurrences in AIDS patients, may predispose thromboembolic complications,[4,5] plasma levels of antithrombin III and protein C activities were also evaluated using chromogenic substrate-based assays, according to the manufacturer instructions (Boehringer Mannheim, Germany). Data were compared by the Mann-Whitney U test. The Spearman rank test was used to evaluate the correlation between parameters. A p value <0.05 was considered to be statistically significant. Our results, as reported in Table 1, suggest that HIV-infection is characterized by hemostatic disorders, such as elevated plasma levels of F1+2, FbDP and PAI-1 activity, and lower plasma levels of protein C activity, usually considered as risk factors for thrombosis in the general population. In particular, F1+2, a sensitive marker of endogenous thrombin generation,[6] and FbDP, an index of unopposed plasmin activity,[7] were found to be significantly correlated in our group of patients, as previously reported in HIV infection.[2]

Table 1. Plasma levels of prothrombin fragment 1+2 (F1+2), antithrombin III (AT III), protein C, fibrin degradation products (FbDP) and plasminogen activator inhibitor (PAI-1) in 22 HIV-infected patients and in 20 age- and sex-matched healthy individuals. Results are given as median with their range.

	HIV- infected patients (n=22)	*Healthy controls (n=20)*	*p*
F 1+2	1.30 (0.68-2.45)*	0.90 (0.40-1.27)	p<0.0002
AT III (%)	103.60 (68.00-142.00)	104.00 (86.00-112.00)	n.s.
protein C(%)	74.41 (26.10-132.20)	99.15 (80.00-117.60)	p<0.0003
FbDp (mg/mL)	1.21 (0.28-2.40)*	0.29 (0.10-0.48)	p<0.001
PAI-1 (AU/mL)	10.41 (7.00-21.00)	4.50 (1.00-9.00)	p<0.0001

**Correlation between F1+2 and FbDP plasma levels: r=0.43, p<0.05.*

On the other hand, it has been suggested that a lower protein C activity may affect thrombotic events when associated with other hypercoagulable conditions (thrombin generation, fibrinolytic shut-down, inflammation, etc.).[8] The mechanism responsible for the enhancement of procoagulant properties and impairment of fibrinolytic capacities in HIV infection is still being studied. However, the loss of endothelial integrity due to HIV infection itself has been suggested as the cause[9,10] and could explain the higher levels of PAI-1 activity we found in AIDS patients. In conclusion, our preliminary results show that HIV infection is associated with an on-going prothrombotic state. We think that this condition should be taken into account, especially when septic events occur as complications, since infectious agents and inflammation mediators have been shown to shift the coagulation-fibrinolysis equilibrium of endothelial cells towards fibrin formation.[4]

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References

1. Toulon P, Gris JC, Candia N, et al. Increased plasmin generation and activity in HIV-infected patients: in vivo rather in vitro activation of the fibrinolytic system. Fibrinolysis 1994; 8(Suppl 2):128-31.
2. Toulon P, Gris JC, Candia N, et al. Activation of coagulation and