CORRESPONDENCE

RECOMBINANT INTERFERON α IN THE TREATMENT OF POLYCYTHEMIA VERA

To the Editor:

We read with interest the recently published article by R.T. Silver regarding the use of recombinant interferon α (r-IFNα) in the treatment of polycythemia vera (PV). We report here our data and comments regarding 11 consecutive PV patients treated with r-IFNα between November 1988 and March 1990. We think that our experience could be useful in providing additional insights into Silver's data. Our patients, diagnosed according to PV Study Group criteria, were 6 men and 5 women, ranged 16 to 79 years (mean, 57 years), all previously managed by either phlebotomy (6 patients) or hydroxyurea (5 patients). r-IFNα was administered at 3 × 10⁶ U/min daily continually for 6 months and at 3 × 10⁶ U/m. three times a week for the subsequent 6 months. Clinical and hematologic response, evaluated after the first 6 months of treatment, was defined by us as: grade I (normalization of hematocrit [Hct], hemoglobin [Hb], white blood cells [WBC], platelets [Plt], and spleen size), grade II (persistance of any of the following: Hct >50%, Hb >16 g/dL, WBC >10 × 10⁹/L, Plt >400 × 10⁹/L, spleen 1 to 5 cm below left costal margin); grade III (no change or disease progression). Five patients (45%) achieved grade I, four (36%) grade II, and two (18%) grade III response (no change). No hemorrhagic or thrombotic episode, observed in some patients before IFN treatment, was recorded during the study and phlebotomy was not required in any case (including the two non-responder patients). The treatment was substantially well tolerated. Side effects (myalgia, anorexia, fatigue) were complained of only in older patients (over 70 years) despite paracetamol administration. All of these symptoms, however, completely relieved after r-IFNα reduction (50% of the initial dose) or temporary discontinuation.

Even if in our experience the doses and the route of r-IFNα administration were different with respect to Silver's, we agree that r-IFNα may be regarded as a promising therapeutic approach in the management of PV, especially in younger patients, who in our study tolerated the treatment better than the older patients. In addition, the opportunity to have an agent able to reduce not only erythrocytosis but also thrombocytosis would be of great relevance, mainly for younger patients who are considered at high risk of developing vascular accidents within the first years of diagnosis.

Finally, r-IFNα, contrary to myelossuppressive agents, is not leukemogenic. This finding is of particular importance for the control of PV patients who are expected to have a long life expectancy. In our experience and Silver's, no significant change in narrow hypercellularity or reticulin was observed after 1 year of r-IFNα treatment. Moreover, we wish to draw attention to some of our laboratory immunologic data on the behavior, before and after r-IFNα treatment, of peripheral T-subset count. We observed after r-IFNα treatment, especially in those patients who achieved grade I and II response, a significant reduction in both mature (CD3⁺: 1.1 × 10⁶/L, P < .01) and helper/inducer (CD4⁺: 0.8 × 1.49 × 10⁶/L, P < .01) T lymphocytes, with CD4⁺/CD8⁺ ratio improvement (3.0 vs 2.1). In regard to suppressor/cytotoxic (CD8⁺) and natural killer (CD57⁺) cell count, a moderate, although not significant, increase after r-IFNα treatment was also observed. Such immunologic data, even if deserving of more extensive evaluation, are speculative in the study of the mechanism of cytoreductive effect exerted by r-IFNα, considering the recognized role played by T lymphocytes in the regulation of hematopoiesis. In this regard, it could be of interest for us to know if Silver also evaluated the cellular immunologic status in his patients. Indeed, we believe that in PV, as in other myeloproliferative disorders, both functional and quantitative changes of immunoregulatory lymphoid cells, potentially related to the mechanism of myeloproliferation, may occur. Therefore, investigations in this direction should be performed because such studies could bring about a better understanding of the therapeutic effect of IFNs also regarded as an immunomodulating agent.

In conclusion, on the basis of our experience we agree with Silver and we deem that r-IFNα may be regarded as a promising agent useful both for the clinical and biologic management of PV.

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RESPONSE

I enjoyed reading the letter by Cacciola et al because it is pleasant to receive confirmation of a new form of treatment that obviates some of the shortcomings of the time-honored therapies for a familiar disease. Since the initial reports of treating polycythemia vera (PV) with recombinant interferon α (rIFNα), I have treated three more patients, each of whom had received prior...
32P or hydrea. Two were anemic and in the cellular phase of myelofibrosis; both had significant regression of spleen size and restoration of normal hematocrits after rIFNa. The third patient had "active" PV and is now in hematologic remission not requiring phlebotomy. All three patients have remained on low doses of rIFNa, approximately $2.0 \times 10^6$ units three times a week and have tolerated the medication without significant side effects. With respect to the two non-responders in the letter by Cacciolo et al, it would be of interest to know if the marrows showed significant fibrosis and/or sclerosis. In my experience, if such advanced changes occur in the marrow it is unlikely that significant hematologic change or clinical regression of splenomegaly will occur. Route of administration is not likely to be related to response because no significant difference in blood levels occurs whether rIFNa is administered intramuscularly or subcutaneously.

I did not evaluate the cellular immunologic status of my patients because abnormalities of immune regulatory function have not been considered an inherent pathogenic defect in the myeloproliferative diseases. According to my calculation of the data provided by Cacciolo et al, the CD4+/CD8+ ratio did not improve but decreased from 11.5 before rIFNa to 2.7 after rIFNa. One wonders whether CD+ monocytes or other non-T cells were also measured by them. Moreover, Foa et al reported that after treatment of hairy cell leukemia with rIFNa there was observed an increase in CD3+, CD4+, and CD8+ circulating lymphocyte subsets and an improved CD4+/CD8+ ratio. These changes were not considered to be related to reduction of hairy cells per se.

Future studies will hopefully resolve the effect of lymphocyte subset changes and clinical remission in patients with PV and other myeloproliferative diseases treated with rIFNa. At the present time, I believe rIFNa is active in PV because of its as yet undefined interrelationship with cytokines involved in hematopoietic control mechanisms, including platelet-derived growth factor, rather than effecting change in subsets of T cells.

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