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LONG-LASTING EFFECT OF CYCLOSPORIN-A ON ANEMIA ASSOCIATED WITH IDIOPATHIC MYELOFIBROSIS

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ABSTRACT

Some reports suggest that immunologic mechanisms may play a role in the pathogenesis of anemia in idiopathic myelofibrosis (IMF). Herein we report the case of a transfusion dependent IMF patient with psoriasis in whom cyclosporin-A (CyA) treatment for skin lesions (200 mg/day) was associated with long-lasting correction of anemia. After 2 months of CyA therapy the patient's Hb level increased and he became transfusion free in 4 months. After 12 months immunosuppressive therapy was discontinued due to renal toxicity, yet the Hb level remained stable for an additional 12 months. The patient is currently being administered CyA at a reduced dosage because of mild renal impairment along with transfusional support consisting of a median of 2 red cell units/month. Altogether the patient received no transfusional support for 36 months. This case, as well as other reports, suggests that the issue of immunosuppressive treatment in IMF anemia deserves further investigation.

Key words: cyclosporin A, anemia, idiopathic myelofibrosis

Idiopathic myelofibrosis (IMF) is a chronic disorder of pluripotent stem cells primarily affecting people over 50 years of age and characterized by marrow fibrosis, splenomegaly and anemia.[1] Since no form of conventional therapy has proven to prolong survival or significantly modify the pathogenetic process, the majority of patients eventually progress to severe transfusion dependence after a variable period of time.

Some reports in the literature suggest that immunosuppressive therapy may reduce the transfusional need in some IMF patients, thus supporting the hypothesis that immune mechanisms may play a pathogenetic role in the progression of the disease.[2-4] We report the case of a transfusion dependent IMF patient with psoriasis in whom CyA treatment for the skin disease was associated with long-lasting correction of anemia.

Case report

A 65-year-old male was referred to us in February 1992 for severe anemia with splenomegaly and hepatomegaly (4 and 3 cms below costal margin respectively). Blood test results were as follows: Hb 6.3 g/dL, RBC 1.9×10^{12}/L, MCV 89 fL, reticulocytes 2.5%, WBC 6.3×10^{9}/L (N 57%, L 27%, M 8%, metamyelocytes 5%, myelocytes 3%), Plt 250×10^{9}/L; some erythroblasts and poikilocytic red cells were also present. Serum LDH and erythropoietin levels were increased. Marrow aspiration proved unsuccessful (dry tap). At bone biopsy, cellularity was 40%; megakaryocytopoiesis and granulopoiesis were hyperplastic; reticular fibers were markedly increased. A diagnosis of IMF (pathologic stage III) was formulated.

Between February and June 1992 he received recombinant human erythropoietin (4000 U/day) and interferon-α2-b (3 MU/day). This treatment did not modify the hematological parameters or the transfusional need. Therefore only transfusional support (a median of 4 packaged red blood cell units monthly) was provided until September 1993 when oral cyclosporin A (200 mg/day) was started for worsening diffuse maculopapular psoriatic skin lesions. During the following months the psoriatic lesions disappeared and his Hb levels unexpectedly began improving. In December 1993 he became transfusion free. In December 1994, after 15 months of treatment, CyA was stopped due to an increase in serum creatinine (>1.5 mg/dL). However, Hb levels remained above 10 g/dL for 12 more months without any further treatment. As of December 1995 the patient has received intermittent CyA treatment with frequent breaks due to impaired renal function, and since November 1996 he has received an average of 2 red cell units/month (Figure 1).

Discussion

The main pathogenetic mechanisms of IMF have recently been elucidated. In particular, while clonal analysis supports the neoplastic origin of the disease, marrow fibrosis seems to be caused by a reac-

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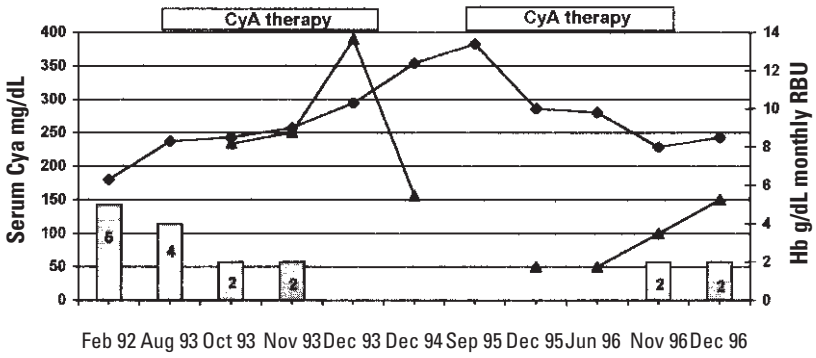

Figure 1. Hb, serum CyA and transfusional need.

tive activation of stromal cells.[5] However, most of the entire process remains obscure and the origin and role of immunological abnormalities that have been described over the last twenty years are not clear. Antinuclear and rheumatoid factor antibodies, lupus-type anticoagulant, positive direct Coombs' test[6] and hypocomplementemia,[7] as well as an increased presence of marrow lymphoid cells and mastocytes which can mediate vascular damage and subsequent marrow fibrosis[8] have been reported. More recently, the serum level of anti-Gal antibodies has been demonstrated to correlate with disease activity. In IMF patients, galactosidic determinants are thought to be expressed by fibroblasts and megakaryocytes.[9] Lewis and Pegrum described the presence of immunocomplexes on leukocytes from 3 patients with IMF.[2] Moreover treatment with chlorambucil and prednisone led to freedom from transfusional dependence in the above mentioned 3 cases. Hashimoto *et al.* demonstrated in mice that CyA may enhance *in vitro* and *in vivo* hematopoietic colony formation, perhaps by decreasing the number of CD8 lymphocytes.[10] These mechanisms may explain the positive action of CyA on certain types of anemia; in fact, CyA corrects both primitive PRCA as well as PRCA secondary to lymphoproliferative disorders[11] and currently stands as the treatment of choice for aplastic anemia.[12] Recently, 10 IMF patients with transfusion dependent anemia received 5 mg/kg/day of CyA. Transfusional needs decreased by more than 30% in four out of the 7 evaluable patients.[3] To our knowledge, no other reports on the efficacy of CyA in IMF have been published.

At diagnosis our patient presented all the clinical and haematological features of typical IMF. The disease was not responsive to α-interferon and erythropoietin, thus anemia progressively worsened and the patient became heavily transfusion dependent. The marked improvement in erythropoiesis associated with CyA treatment occurred early (he became transfusion free after only 4 months) and lasted for 24 months. His Hb levels remained stable for 12 months [illegible] RBU; ▲ serum Cya; ◆ Hb ued. The CyA dosage employed was associated with therapeutic serum levels and acceptable renal toxicity; however, a progressive increase of creatinine levels after 12 months of therapy suggested interrupting therapy. The complete transfusional response we observed seems to indicate that CyA is able to modify certain immunologic mechanisms that may have negatively affected erythropoiesis.

Further trials are needed to clarify the role of CyA and other immunosuppressive agents in the management of anemia in these patients and to assess the immunologic parameters that can predict a response.

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