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To the editor:

Serious myeloproliferative reactions associated with the use of thalidomide in myelofibrosis with myeloid metaplasia

Current treatment in myelofibrosis with myeloid metaplasia (MMM) is inadequate: only a small proportion of patients derive benefit from bone marrow transplantation, splenectomy, or drug therapy.[1] We have recently demonstrated a prognostically detrimental increase in bone marrow microvessel density in the majority of patients with MMM.[2] Because thalidomide may inhibit angiogenesis,[3] its therapeutic activity in MMM is worth investigating.

Before initiating a currently ongoing phase II treatment trial with thalidomide in MMM, we had piloted the drug in 6 patients (age range, 41-71 years; 3 males, 3 females) with symptomatic disease under a compassionate-use protocol approved by the institutional review board. Treatment in all patients was initiated at a daily oral dose of 200 mg, and further dose increments were not tolerated. The duration of treatment ranged from 9 days to 9 months. Of the 6 patients, 3 had concomitant treatment with a cytoreductive agent and were therefore not eligible for accurate assessment of the thalidomide effect on blood counts or spleen size. The remaining 3 patients were treated with thalidomide alone a minimum of 2 months after discontinuing previous specific therapy. The effect of treatment in these 3 patients is as follows.

One patient experienced severe upper left quadrant pain and fever that suggested a splenic infarct after only 9 days of treatment with thalidomide, without associated changes in blood count or spleen size. The second patient had a marked increase in both his previously stable peripheral platelet count (277-1082 $\times$ 10^9/L) and his leukocyte count (7.2-23.6 $\times$ 10^9/L) after only 20 days of treatment with thalidomide (200 mg/day) and required short-term therapy with hydroxyurea. The platelet count increased (152-440 $\times$ 10^9/L) also in the third patient during treatment with thalidomide and returned to baseline after cessation of therapy (9 months at 50 mg per day). The last-mentioned patient also had a durable increase in hemoglobin level (10.9-13.3 g/dL).

The preliminary observations from our current phase II study confirm probable drug-related steep increases in platelet and leukocyte counts in some patients. These changes occurred in the initial 4 to 8 weeks of treatment with thalidomide and were often associated with marked basophilia. We have documented the development of pericardial effusion secondary to extramedullary hematopoiesis in one patient. The mechanism of action and net effect of this biologic activity remain to be determined. But the potential for precipitation of serious disease-related complications exists, and the use of this drug outside a protocol setting is discouraged.

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To the editor:

Fourteen years' follow-up of an autoimmune patient lacking the CD3γ subunit of the T-lymphocyte receptor

A familial defect of T-cell receptor (TCR)/CD3 complex expression by T lymphocytes, due to a selective deficiency of the CD3γ subunit, was reported in 1986.[1,2] Two brothers (V and D) had inherited mutations in both the paternal and maternal CD3γ genes that severely truncated the protein.[3] V had very low counts of peripheral blood $CD3^+$ cells and a low density of TCR/CD3 molecules per cell and a severe combined immunodeficiency and autoimmune enteropathy with gut epithelial cell autoantibodies

Table 1. Major immunological data since 1995

	Dec 1995	Nov 1996	Feb 1997	Mar 1998	Feb 1999	Jan 2000
Lymphocytes*	1100	838	970	1014	1090	1215
CD cells†						
CD4	47 (39-56)	42 (36-56)	48 (36-56)	44 (36-56)	47 (36-56)	50 (36-56)
$CD4^+CD45R0^+$	41 (15-29)	39 (10-27)	47 (10-27)	42 (10-27)	40 (10-27)	47 (10-27)
$CD4^+CD45RA^+$	3 (13-35)	6 (10-35)	3 (10-35)	3 (10-35)	3 (10-35)	3 (10-35)
CD8	9 (15-27)	5 (13-31)	9 (13-31)	7 (13-31)	4 (13-31)	7 (13-31)
Total immunoglobulin‡						
IgG‡	609 (697-1593)	—	594 (697-1593)	609 (697-1593)	671 (644-1436)	688 (644-1436)
IgG2	90 (140-440)	—	147 (95-468)	142 (95-468)	148 (95-468)	146 (95-468)
IgM	39 (39-330)	—	37 (39-330)	38 (39-330)	39 (55-206)	40 (55-206)

Previous data have been published elsewhere.[9] Phenotype and T-cell activation results (using mitogens and antigens) are at present similar to those reported before.[9] —indicates data not determined.

*Lymphocytes are expressed in number per microliter.

†Each CD cell entry is expressed in percentage of positive cells (range of normal values for aged-matched controls in brackets). A severe decrease in the number and function of $CD4^+CD45RA^+$ and cytotoxic ($CD8^+$) lymphocytes is maintained, whereas $CD4^+CD45R0^+$, B, and NK lymphocytes are unaffected.[9] These data allow us to propose a model where CD4 or CD8 molecules interact with the TCR/CD3 complex during antigen recognition through the CD3δ or the CD3γ protein of the complex, respectively.[3] This also correlates with previously obtained data suggesting that αβδεζ complexes are biochemically stable (albeit epitopically altered) and may reach the cell surface in certain circumstances.[4]

‡Immunoglobulins expressed in mg/dL (range of normal values for aged-matched controls in brackets). IgG1, IgG3, IgG4, and IgA levels are always into normal ranges.

(GECA, cytoplasm 1/16, and brush border greater than 1/64). He died at 32 months of age after severe infections and autoimmunity. Still-living sibling D shared the same genotype regarding CD3γ but had milder laboratory immunological and clinical parameters.[4]

D was born in 1981 and began showing clinical symptoms at 12 months of age, including infrequent episodes of repeated Gram-positive and -negative bacterial infections (easily controlled), asthma, diarrhea (which spontaneously disappeared after 6 years), vitiligo, and atopic eczema. A lymphocytary meningitis of probable viral origin (which was quickly overcome) and a mild dilated cardiomyopathy (DCM; probably secondary to unrecorded viral infections) with slight valvular insufficiency were diagnosed at the age of 11 years. Otherwise, D has had a normal development and life (including playing frequent short football matches) and is currently 18 years old.

Table 1 summarizes D's most relevant immunological parameters since 1995. Mean $CD3^+$ cells percentage remains approximately 20% lower in D (ranging from 44% to 57%) than in normal controls (ranging from 60% to 80%), and the surface density of CD3 molecules per cell is 4 times lower in D than in normal controls. Serum autoantibodies were never found before June 1999, when antityroglobulin (185 IU/mL; normal range, 0-89 IU/mL) and antithyroid peroxidase autoantibodies (251 IU/mL; normal range, 0-41 IU/mL) appeared. They were also positive in January 2000 and have been maintained so until this writing.[5] Thyroid hormones (T4, free T4, and TSH) are normal,[6] and thyroid clinical symptoms are absent. Several D alterations (vitiligo, DCM, specific thyroid autoantibodies) may certainly have an organ-specific autoimmune etiopathogeny.[7] These autoimmune anomalies may be directly related to the CD8 cytotoxic/suppressor−CD4 lymphocyte disbalance and to the persistent high numbers of memory T-cell clones ($CD4^+CD45R0^+$) (Table 1). Autoantibodies against GECA, intrinsic factor, insulin, gliadin, kidney glomerular membrane, islet cell, antinuclear, double-stranded DNA, RNP, SSb, Sm, Ro, Scl-70, mitochondrial, smooth muscle, epithelial basement membrane, centromere, parietal cell, intercellular substance, striated muscle, and adrenal antibodies have been repeatedly negative.[5,8]

Previous studies showed that the γ chain is the CD3 component that interacts with the αβ TCR heterodimer. But our data support that a CD3 chain other than γ may also associate to αβ (ie, the highly homologous δ).[4] This could explain D's relatively mild clinical course and cellular phenotype (Table 1). Also, redundant and overlapping functions among proteins of the immune system permit the existence of healthy but immunodeficient individuals, the best known being congenital C2, IgA, HLA class I, and adenosine deaminase deficiencies. Immune function is apparently sufficient for the survival of the CD3γ-lacking D patient, but continuing a close follow-up will enable us to determine the real importance of adaptive versus nonadaptive immune mechanisms throughout an individual's life and to study the mechanisms that relate autoimmunity and immunodeficiency.

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