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Complete Recovery From Refractory Immune Thrombocytopenic Purpura in Three Patients Treated With Etanercept

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Management of patients with immune thrombocytopenic purpura (ITP) who have persistent, severe, and symptomatic thrombocytopenia following splenectomy is difficult and empirical. No single agent or regimen provides long-term success for most patients, and for most treatments it is difficult to assess whether benefits outweigh risks. We report three consecutive patients with critical chronic refractory ITP, who responded promptly and completely following treatment with etanercept, an inhibitor of tumor necrosis factor-alpha. These patients had failed 6–11 previous treatments. In the first patient, etanercept was given for its approved indication: a flare of co-existing rheumatoid arthritis. The next two patients were treated with etanercept because of successful outcomes in the previous patients. Although etanercept appeared to be effective treatment for ITP in these 3 patients, the experimental nature of this treatment and the potential risks must be emphasized. On the basis of these case reports, a clinical trial has been initiated to systematically evaluate the efficacy and risks of etanercept in the management of children and adults with chronic ITP. Am. J. Hematol. 73:135–140, 2003. © 2003 Wiley-Liss, Inc.

Key words: immune thrombocytopenic purpura; ITP; etanercept

INTRODUCTION

Management of patients with critical complications of chronic, refractory immune thrombocytopenic purpura (ITP) is difficult and empirical [1–3]. Many treatment strategies have been proposed with reports of success, but for none of these treatments has efficacy been documented in a randomized clinical trial. Many chemotherapeutic agents used for patients with chronic refractory ITP may cause marrow suppression, and it remains unclear whether benefits of these agents outweigh their potential risks. None of the current strategies cause responses in a majority of patients who have persistent severe thrombocytopenia following splenectomy. Therefore, management of patients with chronic refractory ITP remains a dilemma.

We report here three patients with chronic refractory ITP who apparently responded to etanercept, achieving normal platelet counts which have persisted for 18–19 months after discontinuing all treatments, including etanercept, in 2 patients and for 38 months while continuing etanercept alone given for rheumatoid arthritis in 1 patient. Etanercept is a recombinant fusion protein of the extracellular portion of P75 tumor necrosis factor-alpha (TNFα) receptor and the Fc portion of human IgG_1 developed and approved for use in rheumatoid arthritis and psoriatic arthritis in 1998. In our first patient (Patient

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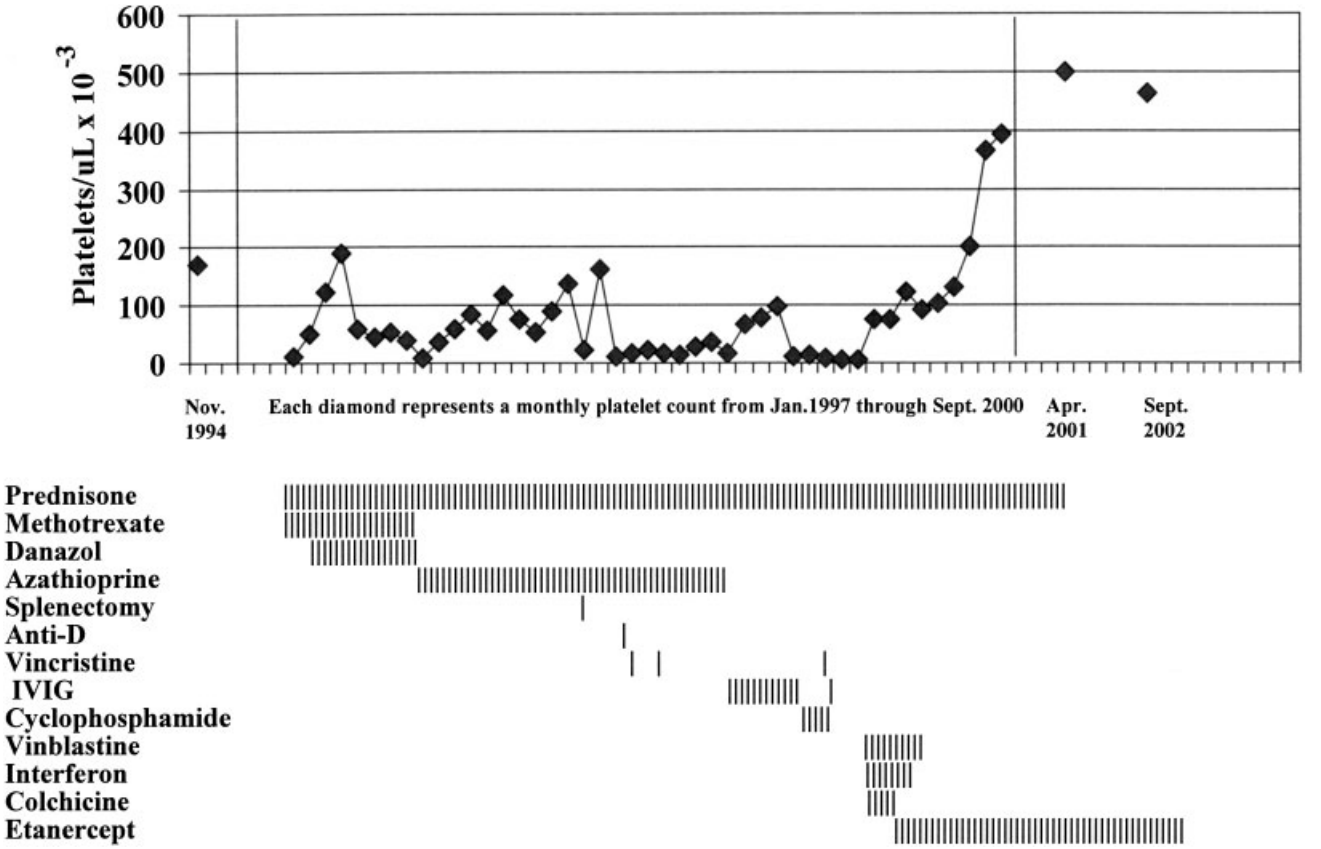

Fig. 1. Clinical course of Patient 1. Platelet counts are presented in three segments: a platelet count in November 1994 prior to the diagnosis of ITP; the clinical course with monthly platelet counts from the diagnosis of ITP January 1997 through September 2000; and follow-up platelet counts in April 2001 and September 2002. The treatment modalities are shown below the figure, with etanercept beginning in February 2000. Etanercept continues to be given once weekly for her rheumatoid arthritis.

1), etanercept was given for a flare of rheumatoid arthritis and recovery from co-existing severe chronic, refractory ITP was incidentally noted. Based on this observation, etanercept was used in a second patient (Patient 2) with very severe ITP who had critical complications and who had been refractory to all previous treatments. Then, on the basis of the apparent success in the first two patients, etanercept was used in a third patient (Patient 3) with severe ITP who had been unresponsive to multiple treatments and had had intracranial hemorrhages. Prior to administration of etanercept for treatment of ITP in Patients 2 and 3, the experimental nature of this treatment was discussed. The apparent success of etanercept in inducing complete responses in these three consecutive patients forms the basis of this report.

CASE REPORTS

Patient 1

Patient 1 is currently a 64-year-old white woman who has had active rheumatoid arthritis since 1991. In January 1994 she had breast cancer treated with mastectomy and adjuvant chemotherapy, completed in November 1994. Her platelet count in November 1994 was normal. In January 1997 she developed extensive ecchymoses and petechiae with a platelet count of 11,000/μL (Fig. 1). There was no splenomegaly, and her hematocrit and white blood cell count were normal. A bone marrow aspirate and biopsy specimen were unrevealing, and there was no evidence of recurrent breast cancer, supporting the diagnosis of ITP. At that time, she was receiving methotrexate, 10 mg/week, and prednisone, 10 mg/day, for rheumatoid arthritis. The prednisone dose was increased to 60 mg/day, and an initial response was seen as her platelet count rose to 119,000/μL with resolution of petechiae and ecchymoses. Danazol was added in February 1997 as the prednisone dose was tapered and the platelet count continued to increase to 190,000/μL. She continued to receive prednisone and danazol until September 1997, when the platelet count fell to 11,000/μL. Azathioprine was then started, and methotrexate and danazol were discontinued. She maintained satisfactory platelet counts on this regimen until July 1998, when the platelet count fell to 23,000/μL; at that time a splenec-

tomy was performed. Her peak platelet count immediately after splenectomy was 161,000/μL; but then the platelet count remained less than 45,000/μL while she was continued on azathioprine and prednisone. She received anti-D in September 1998 and vincristine on two occasions in October and December 1998 for platelet counts less than 20,000/μL. Azathioprine and prednisone were continued until April 1999; then azathioprine was stopped and intermittent IVIG was initiated. Another bone marrow examination in May 1999 was consistent with the diagnosis of ITP. Multiple courses of IVIG over the following 5 months produced a maximum platelet count response of 97,000/μL. Two doses of cyclophosphamide, 1,500 mg each in September and October 1999, failed to produce a response. Colchicine, interferon, and vinblastine were started in December 1999; these agents were continued for 2–4 months with platelet counts increasing to 76,000–123,000/μL. From late 1997 through 2000 she was maintained on prednisone, 10–40 mg/day, for her rheumatoid arthritis as well as for her ITP.

Etanercept, 25 mg administered subcutaneously twice weekly, was added in February 2000 due to a flare of her rheumatoid arthritis symptoms. In April etanercept became her only medication, in addition to prednisone, and her arthritis symptoms resolved. While on etanercept her platelet count rose to 200,000/μL in July 2000 and continued to rise to 394,000/μL in September 2000. Etanercept was then decreased to 25 mg once weekly in August 2000, and prednisone was stopped in April 2001. Her most recent platelet count was 486,000/μL on February 6, 2003. She continues to receive once-weekly etanercept for her rheumatoid arthritis.

Comment. Patient 1 had had persistent thrombocytopenia for 3 years; during this time she had a splenectomy and 10 other treatments. Although she had a partial response when vinblastine, interferon, and colchicine were given, she never had a sustained, complete response to any regimen. Etanercept was started 3 years after the diagnosis of ITP for a flare of her rheumatoid arthritis. Five months after beginning etanercept, her platelet count increased to normal and has remained normal for over 3 years, with continuing etanercept as her only treatment. Her history of breast cancer treated with adjuvant chemotherapy 3 years before the diagnosis of ITP is probably unrelated to her ITP.

Patient 2

Patient 2 was a healthy 54-year-old man when he was seen by his primary care physician in November 2000 to receive vaccinations prior to a business trip to India. He had noted some easy bruising prior to receiving the vaccinations, and after receiving the injections he developed large ecchymoses. He then developed multiple petechiae and purpura on his buccal mucosa and hematuria. A platelet count on November 6 was 2,000/μL (Fig. 2). Other laboratory data were normal, ITP was diagnosed, and he was given platelet transfusions, IVIG, and methylprednisolone. His platelet count increased to 88,000/μL, his bleeding signs resolved, and he continued to receive prednisone treatment. On November 17, while still receiving prednisone, he developed epistaxis and increased bruising with a platelet count of 3,000/μL. He was admitted to the hospital for platelet transfusions, IVIG, and methylprednisolone, and he had an uncomplicated splenectomy on November 20. On November 23 his platelet count rose to 71,000/μL, however he required an emergency laparotomy that day for intra-abdominal hemorrhage. In spite of IVIG and single doses of vincristine on November 22 through 24, his platelet count remained less than 30,000/μL. On November 27 a bone marrow aspirate was normal. On November 26 he began an eight-day regimen of plasma exchange, and on November 28 and 29 he received cyclophosphamide, 2 g/m^2/day; these failed to increase his platelet count. In December, he was treated with cyclosporine and mycophenolate mofetil and received three doses of rituximab, also with no response. Although he continued to receive multiple platelet and red cell transfusions, varying doses of glucocorticoids, and a further course of IVIG, his platelet count never exceeded 5,000/μL. Because of his severe thrombocytopenia and the previous possible efficacy of etanercept in patient 1, etanercept, 25 mg twice weekly, was started on December 21. He had received only one dose of etanercept when, on December 27, he developed progressive hypoxia and pulmonary infiltrates, requiring mechanical ventilation. Cytomegalovirus pneumonia and colitis were diagnosed by serology and lung biopsy on December 31. These were successfully treated with ganciclovir, and etanercept treatment was resumed. Oliguric acute renal failure requiring hemodialysis and *Klebsiella pneumoniae* sepsis occurred on January 6, 2001. On January 19, after a 63-day hospitalization, he was transferred to a rehabilitation facility for 2 weeks; during these 2 weeks his platelet count increased from 58,000/μL to 324,000/μL. Nandrolone was given in late January for depressed testosterone levels and continued until March 2. On March 21 his white blood cell count rose to 18,000/μL with 60% lymphocytes; flow cytometry revealed T cells consistent with T-cell large granular lymphocytic leukemia (expression of CD2, CD3, CD5, CD7, and CD8 and no expression of CD4). On April 11, 2001, when his platelet count was 275,000/μL and had been normal for 9 weeks, etanercept was discontinued. His ITP has continued to be in remission; his most recent platelet count on November 13, 2002, was 284,000/μL. His T-cell large granular lymphocytic leukemia also remains asymptomatic, and he has never required treatment for his disorder. On November 13, 2002, his hemoglobin was 14.1 g/dL and white blood cell count was 10,700/μL with 64% lymphocytes.

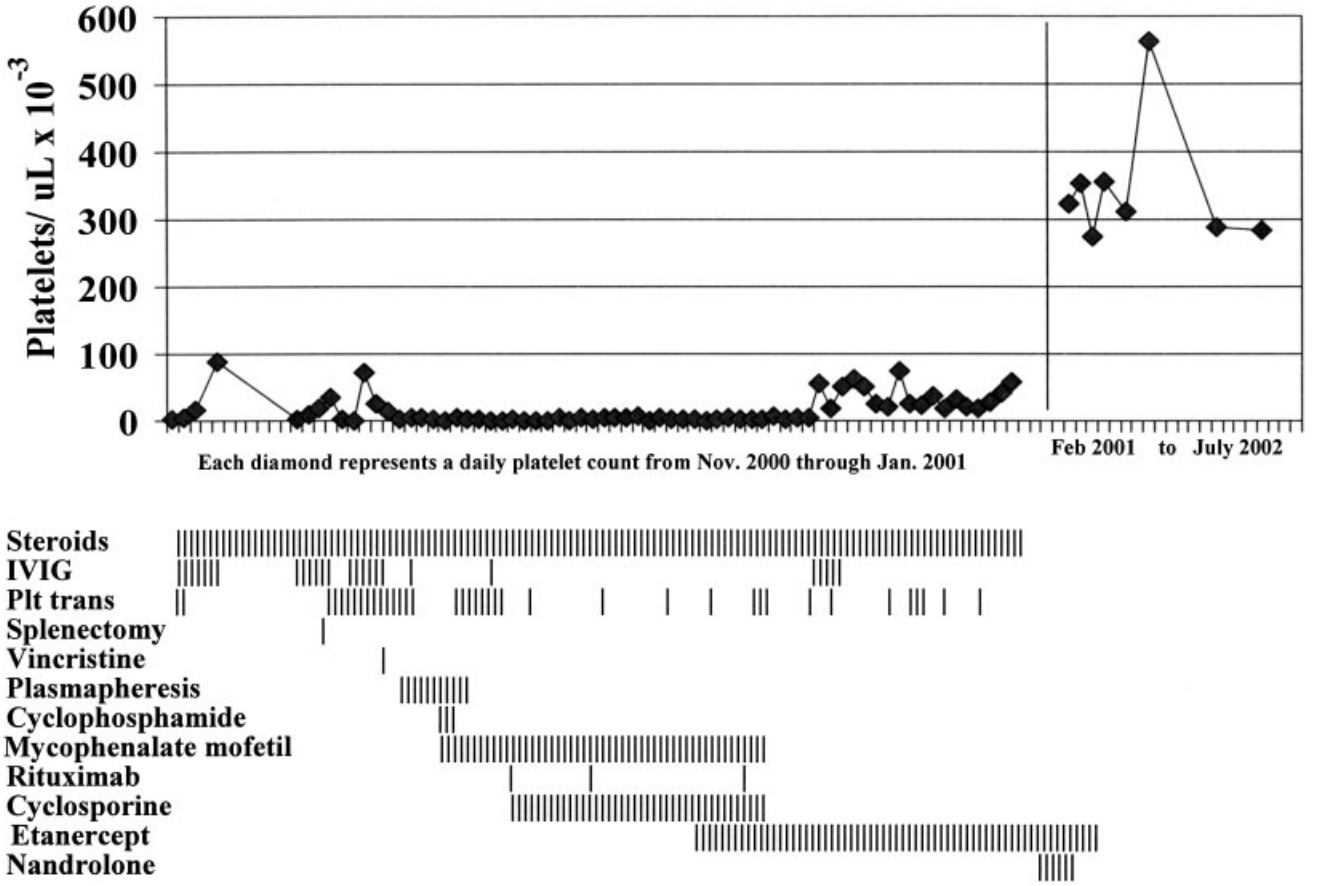

Fig. 2. Clinical course of Patient 2. Platelet counts are presented in two segments: daily, or nearly daily, platelet counts are shown in the left panel from the diagnosis of ITP on November 6, 2000, through January 2001; then monthly, or nearly monthly platelet counts are shown in right panel from February 2001 to July 2002. Etanercept was begun on December 21, 2000, and continued until April 11, 2001.

He now enjoys good health and full activity, including competitive running.

Comment. Etanercept was used in this patient because all previous treatments, including rituximab, had failed and because of the apparent efficacy of etanercept noted in Patient 1. There appeared to be no alternative for this patient. One week after etanercept was begun, after he had received only one dose, this patient became critically ill with cytomegalovirus sepsis as well as bacterial sepsis, complications presumably related to his prior intensive immunosuppressive therapy for ITP. Platelet count recovery began 4 weeks after initiation of etanercept. The nandrolone given for testosterone deficiency may not have had an effect on his ITP; however, androgenic steroids may have some efficacy for ITP, similar to danazol. Etanercept was discontinued after 4 months, and he has remained in complete remission from his ITP for 19 months since etanercept was discontinued. The subsequent development of the lymphoproliferative disease, large granular lymphocytic leukemia, may be related to his ITP. The appearance of large granular lymphocytic leukemia seemed too soon to be a consequence of his cytotoxic therapy, but the experience with long-term consequences of etanercept is minimal.

Patient 3

Patient 3 presented on December 11, 2000, when he was 14 years old, with petechiae after having bronchitis for 1 month. His platelet count was 3,000/μL; ITP was diagnosed (Fig. 3). He received prednisone, 60 mg/day, for 2 weeks without a response. When he developed oral bleeding, anti-D was given with a platelet response to 208,000/μL on January 2, 2001, but 1 week later it fell to 7,000/μL. A bone marrow aspirate/biopsy specimen was remarkable only for megakaryocyte hyperplasia. Further prednisone and IVIG treatments failed to produce a response. On February 1, 2001, he was admitted to the hospital with neck pain, headaches, epistaxis, hematuria, and left facial weakness. His platelet count was 5,000/μL and computed tomography of the brain demonstrated intracerebral hemorrhages with involvement of the cerebellum and right frontal lobe. He had an urgent splenectomy on the day of admission and received 60 units of platelets over the next 8 days, as well as prednisone, IVIG, anti-D,

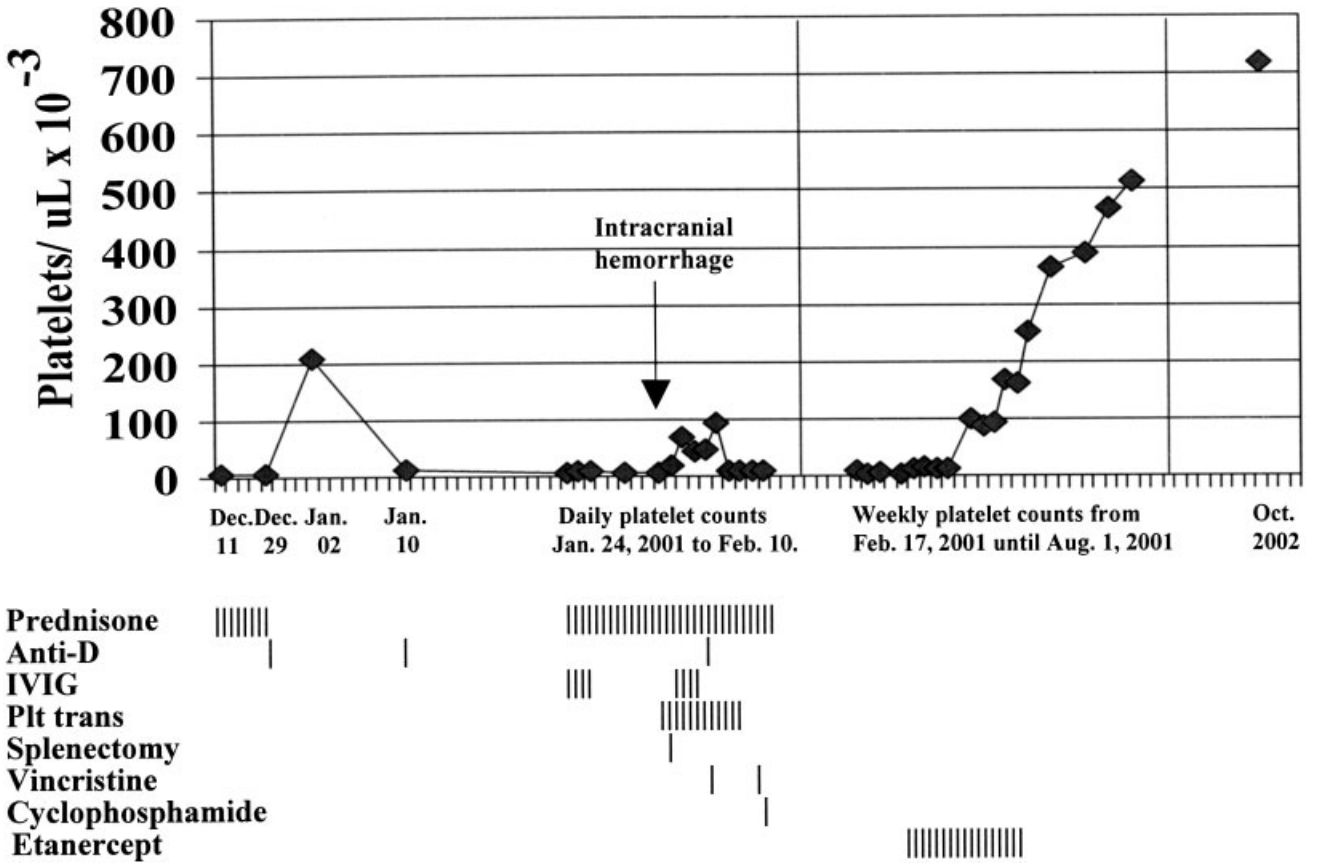

Fig. 3. Clinical course of Patient 3. The clinical course is presented in three segments beginning with the day of diagnosis on December 11, 2000, and continuing with nearly daily platelet counts in the left panel. In the middle panel, weekly platelet counts are presented, and a follow-up platelet count in October 2002 is presented in the right panel.

vincristine, and cyclophosphamide. His peak platelet count was 92,000/μL 4 days after splenectomy. After 16 days in the hospital he was discharged home with no residual neurologic sequelae and a platelet count of 2,000/μL on no treatment. On February 21 he was again admitted to the hospital with left foot and leg pain associated with paresthesias. There was no evidence of a compartment syndrome or hemorrhage on MRI of the lumbar-sacral spine or computed tomography of the pelvis, left thigh, and leg. Throughout March his platelet count remained less than 8,000/μL. His left leg and foot pain resolved in May. Because of continued platelet counts less than 10,000/μL and because of the possibility that etanercept had induced remissions in Patients 1 and 2, etanercept was started on March 16, 2001 at a dose of 25 mg twice weekly. On April 25, 2001, 6 weeks after beginning etanercept, his platelet count increased to 99,000/μL. The etanercept was discontinued after 11 weeks, on May 30, 2001, when his platelet count was 251,000/μL. His last platelet count on October 11, 2002, was 718,000/μL. He now enjoys normal activities, including participating in high school football.

Comment. In contrast to the previous two patients, this patient was relatively asymptomatic and on no treatment for his sustained severe thrombocytopenia at the time etanercept was begun. Etanercept was begun because of the apparent success with the previous two patients and because this patient had suffered severe intracranial hemorrhage and was unresponsive to all treatments except for temporary platelet count increments following splenectomy and multiple platelet transfusions. A platelet count increase was first seen 6 weeks after beginning etanercept, and etanercept was continued for 2 weeks after achieving a normal platelet count. This patient remains in complete remission 18 months after discontinuing etanercept.

DISCUSSION

Although these anecdotes of apparent success with etanercept treatment of three consecutive patients with severe, chronic refractory ITP do not necessarily predict success with future patients, they provide the basis for a systematic evaluation. How etanercept may be effective in ITP is unknown. TNFα levels, as well as levels of two other pro-inflammatory cytokines, interleukin-2 and interferon-γ, are elevated in patients with chronic ITP [4,5]

and may have a role in macrophage activation and platelet destruction in animal models of thrombocytopenia [6,7].

Etanercept is approved for use for rheumatoid arthritis in adults and children and for psoriatic arthritis. It has been used in multiple other autoimmune disorders and other disorders in which TNFα and related cytokines have been postulated to have a pathogenic role. Efficacy has been reported in ankylosing spondylitis [8], immune-mediated cochleo-vestibular disorders [9], Wegener's granulomatosis [10], psoriasis [11], chronic graft-versus-host disease [12], and in one patient with TNF receptor-associated periodic fever syndrome [13]. Etanercept has also been reported to relieve constitutional symptoms of myelofibrosis/myeloid metaplasia [14]. Etanercept has been ineffective in patients with Crohn's disease [15], septic shock [16], and myelodysplasia [17]. In all studies, etanercept appears to be well tolerated and safe, allowing steroid withdrawal in some patients. A retrospective review [18] of 168 patients on etanercept, 25 mg twice weekly, for systemic rheumatic diseases demonstrated that the rate of adverse events was not different from control periods for each patient, which were the times prior to beginning etanercept treatment and for the same duration as the etanercept treatment. We did not interpret any of the complications in our patients to be adverse effects of etanercept, but it must be recognized that etanercept may increase the risk for opportunistic infections.

Because no other agents are consistently effective for patients with chronic refractory ITP and because all agents used have substantial risk, it is appropriate that etanercept be evaluated for its efficacy and safety in the management of patients with chronic refractory ITP. An open-label prospective trial of etanercept for chronic ITP in children and adults has been initiated by one of the authors (M.D.T.).

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