who had not initiated a new pregnancy (n = 88), and to the 96 consecutive new eligible patients. Informed consent to participate was obtained from 180 of these patients; 174 consented during the 3 following months. The 160 women with an ongoing pregnancy at the eighth week were definitively included.

Previous testing for protein Z and anti–protein Z antibodies helped to define, with the 3 main thrombophilic factors, 12 subgroups, and to stratify the 180 informed patients accordingly to them. Pairs of patients were defined as 2 consecutive patients, belonging to the same subgroup. Treatments were randomly and blindly proposed by an independent statistician to the first patient of a given pair and the second patient received the alternative treatment.

No differences, between the 2 treatments, concerning the age of the patients (median, 26 years; range, 18-36 years in the low-molecular-weight heparin [LMWH] group vs 26 years; range, 18-35 years), the weight (median body mass index [BMI], 24.2, range, 21-32 vs 24.1; range, 20.8-32.1), women older than 30 years (12/80 vs 10/80), or obese women (BMI 30 or greater, 5 vs 3) could be evidenced.

All treated patients received the specified treatment, with an excellent compliance, as evaluated by regular questioning, counting of syringes that had been used, or blisters. No patients were lost to follow-up. The primary outcome of the study was analyzed in all included patients. We did not perform any interim analyses.

Finally, we are convinced that roughly 10% of the women with a first pregnancy loss from the 10th week should be treated with prophylactic LMWH and folate intake.

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To the editor:

Fatal case of protothecosis in a hematopoietic stem cell transplant recipient after infliximab treatment for graft-versus-host disease

Two studies recently published in Blood have demonstrated that administration of the anti–tumor necrosis factor antibody infliximab to patients with severe graft-versus-host disease (GVHD) is associated with a high risk of subsequent invasive fungal infections.1,2 We would like to describe an unusual case of disseminated algae infection occurring in a stem cell transplant (SCT) recipient following treatment with infliximab.

A 56-year-old man 562 days after a matched unrelated donor stem cell transplantation was hospitalized for fatigue, rash, and jaundice. He previously had been diagnosed with extensive GVHD of the skin and liver and was receiving prednisone, cyclosporine A, and mycophenolate mofetil. Upon examination, the patient was jaundiced and had multiple pinkish papules on his extremities. Laboratory evaluation showed elevated liver transaminases, significant hyperbilirubinemia, and hyperglycemia. A biopsy of the skin lesions and liver was evaluated and showed significant hyperbilirubinemia and hyperglycemia. A biopsy of the skin lesions and liver was consistent with GVHD. The patient was treated with a methylprednisolone dose of 2 mg/kg per day, infliximab, and extracorporeal photopheresis. Then, 2 weeks later, he became lethargic and developed multiorgan failure and died after 5 weeks of treatment failure.

Klebsiella pneumoniae infection with Prototheca wickerhamii. It seems likely that the patient was colonized with P wickerhamii on the skin or in the colon, and that infliximab facilitated infection dissemination.

In conclusion, human protothecosis is a rare disease, but can cause aggressive and fatal infections especially in severely immunosuppressed patients. The use of infliximab to treat steroid-refractory GVHD likely played a role in this case, and it may be wise to use it with great caution in these patients.

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References

Diamond-Blackfan anemia responding to valproic acid

Diamond-Blackfan anemia (DBA) is a congenital macrocytic anemia characterized by severely reduced erythroid precursors with normal megakaryocytic and granulocytic differentiation. There is also reticulocytoopenia and increased red blood cell (RBC) fetal hemoglobin (HbF). About 25% of patients harbor a mutation on chromosome 19 that involves the gene encoding ribosomal protein S19. Many patients initially respond to corticosteroids, but others may require lifelong RBC transfusions. Other therapeutic modalities include androgens, cyclosporine, interleukin-3, metolopramide, and bone marrow transplantation. We report a case of DBA who markedly improved on valproic acid.

A 19-year-old female was diagnosed with DBA at age 16 months. She received different treatment regimens including prednisone (40 mg daily) for 13 years, and methotrexate (5 mg daily) and cyclosporine (15 mg/kg per day) for the last 3 years. Despite this, she required frequent blood transfusions. She developed autoimmune hemolytic anemia, underwent splenectomy, and lately started to receive least incompatible blood transfusions. One year ago, she received metolopramide (30 mg daily) for 4 months, but transfusion requirements did not improve and the mean hemoglobin level remained at 64 g/L (6.4 g/dL) and reticulocytes, 0.001 (0.1%).

Eight months ago, she was admitted for fever, pneumonia, and urinary tract infection, which were treated with antibiotics. She was still taking prednisone (40 mg daily) for 13 years, and methotrexate (5 mg daily) and cyclosporine (15 mg/kg per day) for the last 3 years. Computed tomography of brain was normal. Valproic acid was started and she was discharged at a dose of 500 mg thrice a day (30 mg/kg per day) with good seizure control. Blood valproic acid levels were therapeutic, ranging between 0.5 and 1.0 g/L.

Since then, the patient has required no further blood transfusions. Hemoglobin level stabilized with a mean value of 126 g/L (12.6 g/dL), and reticulocyte count increased to .04 (4%). Serial HbF levels have been 1.1% to 1.4%, and mean corpuscular volume, 92 to 96.

Valproic acid, also known as 2-propylpentanoic acid or n-dipropylacetic acid, has been used for the treatment of epilepsy since 1978. It is structurally related to butyric acid analogs, such as arginine butyrate, which have been shown to increase HbF. Valproic acid was also shown to increase the percentage of red blood cells that contained HbF in patients with epilepsy. Another study of 4 adults with sickle cell disease treated with valproic acid reported a 3-fold increase in HbF in 3 patients over 2 to 13 weeks.

In another study, valproic acid was as effective as hydroxyurea in increasing the concentration of HbF in patients with sickle cell disease. Furthermore, in patients with sickle cell disease there was a modest increase in both mean HbF concentration and the number of cells containing increased HbF after valproic acid treatment. The mechanism of induction of fetal hemoglobin synthesis by valproate is possibly through modulation of the mitogen-activated protein kinase (MAPK) signal transduction system. In our patient, initiation of valproic acid therapy was temporally associated with an improvement in the hemoglobin concentration, without an increase in HbF. A search of the literature did not reveal any previous use of valproic acid in the treatment of DBA. We recommend considering the use of valproic acid in treating DBA if there is no response to other therapies. Further studies are needed to confirm the potential benefits of this drug in DBA.

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References


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