Linezolid-Induced Pure Red Blood Cell Aplasia

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We report a case of reversible pure red blood cell aplasia that developed in a patient who had received 8 weeks of linezolid therapy.

Linezolid is a recently released synthetic antimicrobial of the oxazolidinone class that has rapidly become an important and widely used drug in the United States. Linezolid is primarily used for the treatment of infections caused by gram-positive organisms, especially vancomycin-resistant enterococci and Staphylococcus aureus (including methicillin-resistant S. aureus).

In animal studies, dogs that received linezolid developed hypersegmentation of megakaryocytes, with slightly decreased peripheral platelet counts, peripheral blood siderocytes, and ringed sideroblasts visible on bone marrow smears [1]. In phase 3 clinical trials of linezolid (600 mg b.i.d. for up to 28 days), the most common adverse events reported were diarrhea, headache, and nausea, which occurred in 9%–11% of subjects [2]. Hematologic adverse effects (i.e., decrease to <75% of baseline levels) were also reported for platelet counts in 10% of subjects and for hemoglobin levels in 7.1% of subjects [2]. We report the development of pure RBC aplasia in a patient who had received oral linezolid for 8 weeks.

Case report. A 52-year-old black man with bullous emphysematous lung disease and the sickle cell trait was admitted to the hospital, the patient had leukocytosis (WBC count, 13.2 × 10³ cells/µL), a normal hemoglobin level (14.5 g/dL), and a normal platelet count (251 × 10³ platelets/µL). There was minimal clinical response to empiric antimicrobial therapy with azithromycin and ceftriaxone and, subsequently, gentamicin, piperacillin-tazobactam, clindamycin, and aztreonam. The patient was transferred to the intensive care unit after becoming hypotensive, and treatment was changed to vancomycin and imipenem (figure 1). The change in treatment was associated with a gradual resolution of fever and leukocytosis, and therapy was then changed to an oral regimen of linezolid and gatifloxacin with continued clinical improvement. On day 38 of hospitalization, the patient was discharged with persistent leukocytosis (WBC count, 15.0 × 10³ cells/µL), anemia (hemoglobin level, 9.6 g/dL), and thrombocytosis (platelet count, 677 × 10³ platelets/µL). The etiology of the anemia was attributed to chronic disease, and thrombocytosis was considered to be a nonspecific response to infection.

During the 2 months after discharge from the hospital, as the patient’s pulmonary infection resolved, his anemia worsened, and the hemoglobin level reached a nadir of 5.9 g/dL. Investigation of the anemia revealed a marked decrease in RBC production (absolute reticulocyte count, 0.003 × 10⁶ reticulocytes/µL [reference range, 0.02–0.15 × 10⁶ reticulocytes/µL]) and no evidence of bleeding (i.e., the results of stool guaiac tests for occult blood were consistently negative) or hemolysis (i.e., serum lactate dehydrogenase and bilirubin levels were normal). A peripheral blood smear showed RBCs with marked anisocytosis and moderate poikilocytosis, with teardrop shapes and ovalocytes. Examination of WBCs revealed a normal differential count and no features of dysplasia. Platelets were normal in size and appearance. Nutritional causes of anemia were considered. The patient had normal serum vitamin B₁₂, RBC folate, and homocysteine levels. Iron studies revealed an increase in serum iron levels to 199 µg/dL (normal range, 35–150 µg/dL) with decreased total iron-binding capacity of 223 µg/dL (normal range, 250–410 µg/dL) and increased iron saturation of 89.2% (normal range, 20%–50%). Erythropoietin levels were appropriately increased, at 1161 mIU/mL (reference range, 4.2–27.8 mIU/mL). The results of serum parvovirus B19 serologic tests were positive for IgG antibodies and negative for IgM antibodies, which is suggestive of prior infection.

A bone marrow study (with aspirate and biopsy specimens) was then performed to determine the cause of the patient’s hypoproliferative anemia. This showed 65% cellular marrow with RBC aplasia, normal platelet development, and moderate eosinophilia. Abnormal pronormoblasts were seen with cytoplasmic vacuoles but with no parvovirus inclusions. Myelo-
Figure 1. Antimicrobials used before linezolid therapy was initiated. Multiple antimicrobials were given to the patient before linezolid therapy was initiated, but none had a significant impact on hematologic parameters. Black bars show periods of administration of antibiotics. Hgb, hemoglobin.

Figure 2. Inhibition of erythropoiesis by linezolid. Linezolid therapy was associated with a worsening of anemia and a profound decrease in the reticulocyte count. Cessation of linezolid therapy resulted in a rapid increase in RBC production and resolution of anemia. Dates show periods of administration of antibiotics. Hgb, hemoglobin.

Erythropoiesis matured fully without dysplasia. The results of immunohistochemical studies using monoclonal antibody for parvovirus B19 were negative. Iron stores were markedly increased.

Linezolid therapy was stopped, and the patient continued receiving treatment with gatifloxacin, lisinopril, montelukast, and inhaler-administered albuterol. During the 10 days after cessation of linezolid therapy, the absolute reticulocyte count increased >50-fold, from $0.007 \times 10^6$ reticulocytes/μL to $0.363 \times 10^6$ reticulocytes/μL. The hemoglobin level increased from 6.1 g/dL at the time of stopping linezolid to 8.6 g/dL at 2 weeks after cessation and 12.1 g/dL at 4 weeks after cessation (figure 2). The patient did not receive any RBC transfusions. Gatifloxacin therapy was stopped 4 weeks after linezolid therapy was stopped.

Discussion. We describe a patient with pure RBC aplasia associated with 8 weeks of linezolid therapy. The patient had rapid recovery of normal erythropoiesis after cessation of only linezolid and continued administration of gatifloxacin and other medications. This patient’s anemia is similar to that reported by Green et al. [3], who recently reported reversible, linezolid-associated hypoproliferative anemia in 3 patients who were receiving linezolid (600 mg b.i.d. for 2–16 weeks). We have shown that the serum erythropoietin level was useful in demonstrating that anemia was due to intrinsic bone marrow failure in our patient, who was recovering from a serious and chronic infection; in this clinical setting, a decrease in the erythropoietin level would be expected. In addition, we were able to exclude parvovirus B19 as a potential cause of the patient’s RBC aplasia.

In their review of postmarketing surveillance data, Kuter and Tillotson [4] state that “it is evident that linezolid was not the sole cause of the (reported) hematologic findings,” including anemia (p. 1013). We are less sanguine. The mechanism of cytopenia is unclear. Linezolid binds to a site on the bacterial 23S rRNA of the 50S subunit, inhibiting translation.
and protein synthesis [2]. Inasmuch as the bone marrow morphology is similar to that seen with chloramphenicol toxicity, which may be irreversible in some cases, it would seem prudent to monitor patients receiving extended therapy. The dramatic effect of linezolid on the reticulocyte count, together with the ease with which the absolute reticulocyte count can be measured, suggests that obtaining a baseline value at the initiation of linezolid therapy could be useful in detecting bone marrow suppression.

References