Effective Treatment of Drug-Induced Agranulocytosis Using Recombinant Human Granulocyte Colony Stimulating Factor in Pregnancy

R. Ritsuto Fujiwaki
T. Toshiyuki Hata
K. Kohkichi Hata
M. Manabu Kitao
H. Hiroshi Furuya
Y. Yuzuru Katoh

Departments of *Obstetrics and Gynecology and bInternal Medicine, Simane Medical University, Izumo, Japan

Key Words
Drug-induced agranulocytosis
Granulocyte colony stimulating factor
Pregnancy, drug-induced agranulocytosis

Abstract
Drug-induced immune system mediated agranulocytosis is a rare but potentially life-threatening condition. There have been only a few reports on drug-induced agranulocytosis during pregnancy. We present a case of agranulocytosis after prolonged intravenous infusion of ritodrine hydrochloride and additional administration of indomethacin suppositories, effectively treated using recombinant human granulocyte colony stimulating factor without any infection in a mother with twin-to-twin transfusion syndrome. Recombinant human granulocyte colony stimulating factor may have a potential use for drug-induced agranulocytosis during pregnancy.

Introduction
Drug-induced immune system mediated agranulocytosis is a rare but potentially life-threatening condition. This complication of drug therapy occurs usually within the first 3 months of treatment and is characterized by a sudden drop of the granulocyte count to almost 0. Nearly all patients develop severe septicemia with or without localized infection and rare critically ill. Following withdrawal of the offending drug, the granulocyte count returns to normal within 1 to several weeks [1]. There have been only a few reports on drug-induced agranulocytosis during pregnancy [2]. To the best of our knowledge, there has been no report on the use of recombinant human granulocyte colony stimulating factor (G-CSF) in the treatment of drug-induced agranulocytosis during pregnancy. We describe a case of agranulocytosis after prolonged intravenous infusion of ritodrine hydrochloride and additional administration of indomethacin suppositories, effectively treated using G-CSF without any infection in a mother with twin-to-twin transfusion syndrome.

Case Report
A 26-year-old Japanese woman, gravida 2, para 2, was admitted to our university hospital for premature labor due to twin-to-twin transfusion syndrome at 22 weeks of gestation. She was...
begun on a regimen of a continuous intravenous infusion of ritodrine, varying from 0.1 to 0.2
mg/min, but contractions did not cease. Therefore, she received additional indomethacin
suppositories, varying from 50 to 150 mg/day. Amniocentesis (four times) was performed for
relief of abdominal pain and discomfort, and the total amount of amniotic fluid removed was
6,600 ml.
On admission, the white blood cell count was 6,900/mm³ with 55% segmented neutrophils, 32%
lymphocytes, and 10% monocytes. Hemoglobin was 9.0 g/dl, and the platelet count was
229,000/mm³. On the 23rd hospital day, the white blood cell count eventually
dropped to 1,600/mm³ with 0% segmented neutrophils, 0% band forms, 52% lymphocytes, 46% monocytes, and 2% basophils. Hemoglobin was 8.7 g/dl, and the platelet count was
310,000/mm³. Bone marrow examination showed hypocellularity with a lack of late gran-
ulocyte forms. Ritodrine and indomethacin were discounted, and broad-spectrum antibiotic
treatment was started. In addition, G-CSF (Sankyo, Tokyo, Japan; 1.5 g/kg/day s.c.) was started.
Two days after G-CSF administration, the white blood cell count was 2,700/mm³ with 0%
neutrophils and rose to 7,100/mm³ with 13% neutrophils, 5% bands, 42% lymphocytes, 26%
monocytes, and 1% basophils 5 days later. On physical examination no splenomegaly was noted,
and no sites of infection were identified. The next day (29 weeks of gestation) she was delivered
vaginally of 2 viable female infants weighing 960 and 740 g, respectively. The complete blood
counts in the 1st (recipient) baby were 7,700/mm³ for white blood cells, 20.4 g/dl for
hemoglobin, and 212,000/mm³ for platelets, and those in the 2nd (donor) baby were 8,900/mm³
for white blood cells, 14.7 g/dl for hemoglobin, and 180,000/mm³ for platelets. The maternal
white blood cell count was 11,800/mm³, with 21 % neutrophils, 7% bands, 23% lymphocytes,
and 25% monocytes. On day 8 G-CSF was stopped. The patient had an uneventful puerperal
course, and no postpartum infectious complications occurred.
Discussion
The diagnosis of drug-induced agranulocytosis was made on the basis of the clinical findings [1].
In this report, the patient was simultaneously exposed to two drugs (ritodrine and indomethacin)
which are known to induce agranulocytosis [2, 3]. It must be stated that definite proof that
ritodrine and/or indomethacin caused the agranulocytosis in our patient is lacking, since
serological testing was not done. However, leukopenia and neutropenia resolved rapidly within
7 days after cessation of both drugs.
Treatment with G-CSF has two beneficial effects: (1) shortening of the duration of complete
agranulocytosis and (2) an accelerated increase of granulocytes during the recovery phase [1]. It
cannot be proved that G-CSF treatment was responsible for the rapid recovery of granulocytes;
however, there are several arguments which suggest that G-CSF treatment may have shortened
the duration of agranulocytosis [1]. The time to recovery is strongly dependent on the number of
granulocyte precursors in the bone marrow. If the bone marrow is hypoplastic, the duration of
agranulocytosis ranges from 7 to 56 (median 14) days. In our patient the bone marrow
immediately before the start of G-CSF therapy was hypoplastic; therefore, it might be expected
that a recovery time is > 7 days. However, in our patient, neutrophils recovered (normalization of
neutrophil count > 1,500/mm³) within 7 days. Wang-Cheng and Davidson [2] reported that
leukopenia and neutropenia resolved very rapidly within 3 or 4 days after cessation of ritodrine
without the use of G-CSF. The reason for this difference of recovery time is currently unknown.
One possible explanation is that granulocyte precursors in the bone marrow in their case might
be present in normal numbers, although these authors did not perform bone marrow examination.
Maternally administered G-CSF has been shown to cross the placenta and induce a peripheral neutrophilia in fetal rats [4]. In our case, the white blood cell counts in both babies were within normal ranges. The reason for this unresponsiveness to G-CSF in our babies is currently unknown. However, time and dose of G-CSF during pregnancy might affect the effect of G-CSF on fetal granulo-poiesis.

References