The Shwachman syndrome (SS) is a rare autosomal recessive disease characterized by exocrine pancreatic failure, growth retardation, skeletal abnormalities (such as metaphyseal chondrodysplasia), recurrent infections and hematological anomalies, the most frequent ones being cyclic neutropenia, anemia and thrombocytopenia.

Given the effectiveness of rHuG-CSF in congenital agranulocytosis we were encouraged to use rHuG-CSF in a case of SS with recurrent infections and significant neutropenia that did not respond to corticosteroids.

**Case report**

A 4-year-old boy, born at full term (birth weight 1,800 g) with an intrauterine growth development of 31-32 weeks showed the following symptoms from birth: frequent episodes of diarrhea, feeding problems, psychomotor developmental delay and a diffuse dermatitis of the scalp and body. At admission (4 months) he presented severe growth retardation (weight and height <<3rd centile), steatorrhea, pancreatic failure, severe psychomotor developmental delay, neutropenia (PMN range 0.15-0.38×10⁹/L) with bone marrow hypoplasia (low cellularity, myeloid/erythroid cell ratio 4.3), without anemia (Hb: 12.9 g/dL) or thrombocytopenia (PLT: 207×10⁹/L).

The patient’s medical history suggested a diagnosis of Shwachman syndrome after cystic fibrosis was ruled out (sweat electrolytes were normal: Na 15mEq/L and Cl 12 mEq/L, as was xylose absorption: xylose 30.7 mg/dL). At the moment of diagnosis, metaphyseal chondrodysplasia (which is associated with the syndrome in 50% of cases and usually appears after 2 years of age) and retinitis pigmentosa (which is also associated with the syndrome in 15% of cases) were not evident. Neutropenia in SS is of the
hyporegenerative type and is often associated with a defective neutrophil mobility that was not present in our case (normal chemotaxis, normal superoxide production after stimulation with Zymosan). The patient had a normal karyotype. An electroretinogram showed a generalized reduction in amplitude consistent with his myopic chorioretinosis. Pancreatic failure was indirectly confirmed by the fact that supplementation with pancreatic enzymes improved linear growth (from <<3rd cent. to 3rd cent.).

High-dose corticosteroid and immunoglobulin therapy (1 g/kg/day for 2 days) failed to increase PMN values (max PMN 0.55×10^9/L) and the child was treated with long-term continuous antibiotic therapy (one year). Any attempt to suspend antibiotic therapy led to a suppurative infection.

At the age of 18 months rHuG-CSF treatment was started at a daily subcutaneous dose of 7.5 μg/kg. This rapidly resulted in an effective stimulation of neutrophils, which reached values up to 6.1×10^9/L, and concomitant bone marrow recovery (higher cellularity, myeloid/erythroid cell ratio 1.5), and complete disappearance of the suppurative clinical features (anal abscess). During the following months, owing to the onset of severe bone pain and in order to avoid maximum effective dosage of rHuG-CSF by administering a daily dose of 7.5 μg/kg once a week. This dosage was then gradually reduced at weekly intervals from 7.5 μg/kg/week to 5 μg/kg/week to 2 μg/kg/week.

During this time (10 months), the child remained free of infections and mean neutrophil values ranged from 0.4-0.69×10^9/L immediately before therapy to 1.2-3.2×10^9/L the day after (Figure 1). In order to evaluate whether rHuG-CSF was responsible for maintaining a protective level of neutrophils and for the spontaneous trend of the white blood cells, rHuG-CSF was discontinued twice in 2 years. During the suspension periods neutrophils decreased progressively (4 weeks after suspension of therapy PMN values were down to 0.2×10^9/L the first time, and 3 weeks after the second suspension PMN were less than 0.2×10^9/L) and suppurative infections recurred (otitis media).

rHuG-CSF treatment was then reintroduced at the weekly minimum effective dose of 2 mg/kg. During the subsequent follow-up periods no suppurative infections occurred and the value of circulating PMN ranged between 0.35-1.05×10^9/L after the second suspension period. No side effects have been reported; red cell and

![Image of Table 1](https://via.placeholder.com/150)

**Table 1. Mean values of PMN×10^9/L during rHuG-CSF therapy.**

<table>
<thead>
<tr>
<th>Time</th>
<th>PMN×10^9/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>before therapy</td>
<td>75 γ daily</td>
</tr>
<tr>
<td>after therapy</td>
<td>75 γ weekly</td>
</tr>
<tr>
<td>without therapy</td>
<td>50 γ weekly</td>
</tr>
<tr>
<td>infection</td>
<td>22.5 γ weekly</td>
</tr>
<tr>
<td>infection</td>
<td>22.5 γ weekly</td>
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![Graph of PMN×10^9/L](https://via.placeholder.com/150)
G-CSF in Shwachman syndrome

platelet counts have remained unvaried.

Discussion

Cyclic neutropenia is one of the main features of SS and it is responsible for the susceptibility of these patients to severe infections. The exact physiopathologic mechanism of this defect is unknown but it appears to be invariably associated with bone marrow hypoplasia and seems to be due to defective maturation of precursor cells. The degree of neutropenia in SS is variable and spontaneous recovery has been described by some authors, although the disorder tends to persist for a long time and life-threatening infections can occur.

Corticosteroids are not effective in the treatment of neutropenia in SS and data are lacking for alternative types of therapy. rHuG-CSF has been successfully used in both acquired and congenital neutropenia (cyclic neutropenia), idiopathic neutropenia and neutropenia associated with glycogen storage disease.

A review of the literature shows only 3 patients affected by SS were treated successfully with rHuG-CSF, but higher dosages (5 mg/kg/day and 1 mg/kg/day) and daily administrations were employed.

In our case neutropenia was very severe (PMN range 0.12-0.38×10⁹/L) and resulted in recurrent and persistent suppurative infections. This convinced us to evaluate the efficacy of rHuG-CSF. The initial dosage was high (7.5 μg/kg/day), as recommended by other authors. However, we believed that lower, intermittent administration might be more appropriate in SS where occasional cases evolve into lymphocytic or nonlymphocytic leukemia, as reported by other authors. Thus, after experimenting with increasingly lower doses, we determined that both neutropenia and infections were adequately controlled with a lower weekly dose of rHuG-CSF (from 7.5 μg/kg/week to 5 μg/kg/week). Interruption of treatment twice during the 2-year follow-up period brought about a steady decrease in the number of neutrophils to below the safety limit, and a recurrence of suppurative infections. It seems reasonable to assume that the improvement in neutrophil count was indeed due to treatment and not to a spontaneous recovery of neutrophils. A low weekly dose seems to be effective at ensuring maintenance of neutrophil values and a symptom-free period.

In conclusion, we suggest that rHuG-CSF used at low weekly doses can be an effective and less expensive way of treating neutropenia in SS.

References