This is the third newsletter of the Severe Chronic Neutropenia International Registry (SCNIR). This newsletter is sent to all physicians who have patients enrolled in the Registry in order to share our data and experience. This issue will focus on recent Registry activity, present data from the second annual Registry regulatory report, and answer some questions that have been raised by practicing physicians. As always, if you have questions, please feel free to contact any of the physicians on the Scientific Advisory Board or, alternatively, either of the Data Coordinating Centers (DCC).

**Report on Registry Activity**

The Registry has experienced positive growth during 1996. As of October 1, 1996 the Registry had 398 actively enrolled patients in 11 countries with an additional 105 non-active patients for a total of 503 patients in the database. Enrollment by country is listed below.

The SCNIR is indebted to those physicians who have enrolled patients and who regularly complete follow-up forms. The receipt of timely data is key to the Registry’s success and enables us to provide an analysis of data to the scientific/medical community on an annual basis. We have seen a positive response to our strategies to improve the timely return of the 6 month follow-up forms and have recently revised the Registry case report forms with the aim of making completion a less time intensive process.

**SCNIR Patient Enrollment by Country**

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<th>COUNTRY</th>
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<tr>
<td></td>
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* through October 1, 1996

**Total Enrollment** 398
Synopsis of Second SCNIR Annual Regulatory Report

The SCNIR enrolls patients with severe chronic neutropenia (SCN), defined as patients having a neutrophil count of less than 0.5 \( \times 10^9 \)/L on at least three occasions in a 3 month period, having a bone marrow aspirate consistent with SCN, and a history of significant infections. The Registry includes patients with a variety of non-malignant causes for neutropenia, classified principally into three broad categories: congenital, cyclic, and idiopathic neutropenia.

During the past year, the Registry initiated a variety of research projects, including the growth and development of patients treated with NEUPOGEN® (Filgrastim), and studies on genetic and molecular mechanisms of SCN. In addition, the Registry facilitated the collection of blood and bone marrow specimens for studies of cellular signal transduction and abnormalities of the G-CSF receptor which involved several investigators. Any participating physicians interested in conducting research using Registry data should contact a DCC office for guidelines on submitting a proposal.

Summary of Clinical Observations

The number of enrolled Registry patients in all three major diagnostic categories continues to grow, roughly proportional to the original enrollment, with congenital neutropenia constituting the most frequent of the three major diagnoses (n=164 or 52.0%). It is followed by cyclic neutropenia (n=65 or 20.6%) and idiopathic neutropenia (n=86 or 27.3%).

With increasing enrollment there is increasing diversity in race/ethnicity. Currently the majority of all patients with data in the Registry (84.5%) are Caucasian, and most (62.6%) are in the pediatric age group (less than 18 years of age). Treatment histories indicate that a variety of therapies have been given to SCN patients. Most treatment data, however, pertains to therapy with NEUPOGEN®; 86.3% of patients for whom treatment data are available now receive this as a primary therapy for neutropenia.

The natural history and treatment outcomes of SCN are not well understood. The Registry serves to clarify many clinical questions in this regard. Observations include the following:

Treatment Responses

Longitudinal data from the SCNIR demonstrates that with continued NEUPOGEN® treatment, an increased neutrophil level, which results in a reduction in infections and inflammatory symptoms, can be maintained for at least 7 years.
Development of Leukemia and Cytogenetic Abnormalities

For patients with congenital neutropenia, the development of cytogenetic abnormalities, myelodysplasia, and leukemia remain the issues of greatest concern. Cases of leukemic transformation were documented in congenital neutropenia patients prior to the use of cytokines (DeVries et al, 1958; Gilman et al, 1970; Lui et al, 1978; Matsaniotis et al, 1966; Rosen and Kang, 1979). Of the published cases of congenital neutropenia, 42% of patients died at a mean age of 2 years secondary to sepsis and pneumonia (Young and Alter, 1994). In the SCNIR 1995 annual report, the median age of congenital neutropenia patients enrolled in the Registry was 10.4 years (range 0.2 to 40.6).

To date, Registry reports of leukemic transformations have occurred only in the congenital neutropenia patients; no leukemic transformations have occurred among patients with cyclic or idiopathic neutropenia. Among the 191 congenital neutropenia patients from the clinical trials, with an average follow-up of 4.7 years, 22 have been reported to develop AML/MDS. The rate of MDS and AML reported in these congenital neutropenia patients in the SCNIR who were treated with NEUPOGEN® for up to 5 years is 1.6 cases per 100 patient-years of exposure; for patients with acquired types of SCN (cyclic and idiopathic), this rate is zero cases per 100 patient-years of exposure.

Cytogenetic abnormalities, including monosomy 7, have been reported in patients treated with NEUPOGEN® who had previously documented normal cytogenetic evaluations. It is unknown whether the development of cytogenetic abnormalities, myelodysplasia, or acute leukemia is related to chronic daily NEUPOGEN® administration or to the natural history of SCN. The SCNIR has recommended annual bone marrow and cytogenetic evaluation in all patients with congenital neutropenia.

Pregnancy and Fertility

The Registry staff, working with Amgen’s post-marketing safety group, have collected information on 11 pregnancies occurring in 9 patients with SCN treated with NEUPOGEN®, all of whom had either cyclic or idiopathic neutropenia. Six of these 11 pregnancies resulted in either a normal birth or a child with cyclic neutropenia, which is known to be inherited in an autosomal dominant fashion. In addition, the Registry has one report of a male patient (a patient with cyclic neutropenia) who fathered a child with cyclic neutropenia. In three other cases, congenital anomalies were detected either during gestation or at birth, and one of these pregnancies, plus two others without known congenital anomalies, resulted in elective terminations. Of the two live births with congenital abnormalities, one had bilateral hydronephrosis and the other a cardiac defect. Both of these developmental abnormalities are relatively common; at present there is no known association with NEUPOGEN® treatment. Surveillance continues regarding the relationship of treatment to pregnancy outcome. In treated patients, advice to physicians and patients continues to be that the effects of NEUPOGEN® on pregnancy and fertility are not yet known.

Growth and Development

New analyses of growth and development parameters show that the percentage of children from the United States with SCN who are over the 50th percentile of weight for height increased with the duration of treatment. These data also show that for children starting treatment before three years of age, the percentage with height over the 50th percentile appears to increase with duration of treatment compared with those starting treatment after three years of age. This is the first evidence that early treatment may benefit early physical development in children with congenital neutropenia who tend to have retarded linear growth. Further monitoring and analyses of these data are ongoing.
**Mortality**

Six patients in the Registry died during this reporting period. These patients died due to either complications of bone marrow transplant performed post diagnosis of MDS/AML (four patients) or infection (two patients).

**Observation of Other Adverse Events**

The incidence and severity of other adverse events prompted for in the SCNIR reporting forms, including thrombocytopenia, splenomegaly, osteoporosis and vasculitis, was found to be consistent with that reported in the Amgen sponsored SCN clinical trials (see NEUPOGEN® Package Insert). No trend for new or unusual adverse events was found during this reporting period.

**References**


Questions Frequently Asked by Treating Physicians

1. What advice should be given to a patient with SCN who is receiving G-CSF and who develops a fever?

Patients with SCN who are responsive to G-CSF have a lower risk of invasive bacterial infection than those patients who are untreated. However response to G-CSF can fluctuate over time and therefore it is recommended that a patient with SCN who is receiving G-CSF have a CBC performed within the first day of onset of fever. The urgency of seeking medical attention must be based on the individual patient’s history of infection, response to G-CSF and any other associated symptoms at the time of onset of the fever.

It should also be noted that G-CSF is not itself a pyrogen, therefore, fever occurring during therapy with G-CSF should not be attributed to the G-CSF itself. A patient on G-CSF may develop infection despite having a good ANC. G-CSF administration should be continued during treatment of infection.

2. How frequently should a patient be monitored with blood counts while receiving G-CSF and when should the dose be adjusted?

When initiating G-CSF treatment, the SCNIR Advisory Board recommends that one aims for an absolute neutrophil count (ANC) of 1.0 to 10 x 10⁹/L. It is important to monitor total white blood cell count and neutrophil count at least weekly until the neutrophil count stabilizes. One then titrates the dose based on clinical response.

Data from the Registry indicates that patients with congenital neutropenia (e.g. Kostmann’s) are being treated with a median dose of 5.6 mcg/kg/day. Those patients with cyclic neutropenia are requiring a median dose of 1.7 mcg/kg/day while patients with idiopathic neutropenia are being treated with a median dose of 1.0 mcg/kg/day. It is important to note that patients with cyclic neutropenia will still have a cyclical pattern to their neutrophil count despite a good response so there may be quite a wide variation in ANC between troughs and peaks.

Once individuals are stabilized on G-CSF therapy, monthly monitoring of ANC during the first year of therapy is recommended. G-CSF dosage may need to be adjusted if there are very high or very low counts obtained. Blood samples should be drawn prior to the daily administration of G-CSF. In our practice, we have found that after the first year of therapy, providing the patient is stable on G-CSF treatment, blood counts may be obtained less frequently (possibly every two to three months).

The aim of G-CSF therapy is to improve the ANC and ameliorate symptoms associated with the neutropenia. The goal is to maintain the patient on the lowest dose of G-CSF necessary to maintain sustained relief of symptoms. Providing the patient is well, G-CSF treatment may be reduced to alternate day administration or occasionally even less frequently.
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