

# Update

This issue of the physician newsletter produced by the Severe Chronic Neutropenia International Registry (SCNIR) summarizes the activity of the Registry for the past year, including a synopsis of the last Annual Report and a report on presentations at the 1997 American Society of Hematology meeting. You will also find answers to questions often asked by health care providers, as well as a list acknowledging all participating physicians from around the world.

## ASH 1998 and Other Registry Activities

The Registry will be well represented at the 1998 American Society of Hematology meeting in Miami with three poster session abstracts and an educational session. Dr. Larry Boxer will present "Severe Congenital Neutropenia, Its Management and Outcome: The Role of the SCNIR" at an educational session on pediatric registries. The abstracts are "Bone Marrow Transplantation (BMT) in Patients with Severe Congenital Neutropenia (SCN) Refractory to G-CSF", C Zeidler, JE Levine et al; "SCF in Children with Severe Congenital Neutropenia", C Zeidler, et al; and "Long Term Safety of Filgrastim (G-CSF) Therapy for Chronic Neutropenias", SE Kinsey, et al. Look for reviews of Dr. Boxer's presentation and the abstracts in the next Update.

The Registry has increased enrollment in the past year by 25% and we continue to enroll approximately ten new patients per month worldwide. Enrollment by country is listed in the table below.

As the Registry continues to grow, we are developing a variety of ways to communicate the results of our research and data analysis to physicians and patients. A newsletter and hand book

## SCNIR Patient Enrollment by Country\*

COUNTRY	NUMBER OF PATIENTS	COUNTRY	NUMBER OF PATIENTS
Australia	40	Italy	17
Belgium	16	Luxembourg	1
Canada	33	Netherlands	8
Germany	59	Spain	15
Ireland	6	Sweden	8
Israel	8	United Kingdom	43
		United States	354
		<b>Total Enrollment</b>	<b>608</b>

\* Through September 8, 1998

for patients and their families will be published soon; the Registry web site is undergoing a major renovation and is now located at a new address: <http://weber.u.washington.edu/~registry>

The bone marrow cell bank initiated in 1997 contains approximately 70 samples and we are interested in continuing to collect samples from congenital and cyclic neutropenia patients. Our goal is to obtain (1) at least one baseline sample, preferably the diagnostic marrow, on each congenital and cyclic patient and (2) annual samples on all congenital patients. These samples will be invaluable for long-term laboratory studies in these patients. Please contact a Registry office to obtain the instructions for sending a bone marrow sample to one of the cell banks.

## Highlights from ASH 1997

### *Clinical Studies*

1997 ASH abstracts included reports from the SCNIR on two sub-groups of patients registered. A report on the long-term treatment of chronic idiopathic neutropenia with G-CSF<sup>1</sup> was presented in a poster session and an abstract appeared regarding patients with Shwachman-Diamond syndrome (SDS) with severe chronic neutropenia.<sup>2</sup>

Regarding patients with idiopathic neutropenia, the registry contained data on 137 patients, of whom 116 had been treated with G-CSF for a median of 2.3 years. The mean infection rate decreased from 20.4 events during the year prior to treatment to 2.4 events during the first year of treatment. The number of infection-free months increased from a mean of 2.9 months at baseline to 8.4 months during the first year of treatment. No patients in this group have developed MDS or AML. G-CSF appears to be an effective long-term therapy for patients with severe chronic idiopathic neutropenia. For a further report regarding dosing of G-CSF in these patients, please see below.

The SCNIR has now collected data on 13 patients with Shwachman-Diamond syndrome (SDS) and chronic neutropenia. Patients with SDS are known to have a predisposition to leukemic transformation; however, the relationship to the severity of the bone marrow dysfunction or its treatment is unclear. In the 13 patients reported, eight had received G-CSF. Of these, 3 patients (23%) have developed deletion of chromosome 7, with one of these transforming to AML. Because of concerns regarding the high risk of leukemic transformation in SDS patients, the SCNIR is now registering patients with SDS, even if they do not have severe chronic neutropenia, in an attempt to learn more about the relationship of bone marrow dysfunction to leukemic risk.

### *The Role of G-CSF Receptor Mutations as a Step in Leukemogenesis*

Investigators in several centers reported on further studies of mutated G-CSF receptors (G-CSF-R) at ASH 1997. These mutations have previously been found to develop in some patients with severe chronic neutropenia and a subset of those patients developing the mutations have developed AML/MDS, as reported previously by the SCNIR.<sup>3</sup> As a result,

interest has been stimulated in further research regarding the potential role of this mutation in both SCN and AML/MDS.

Investigators in two centers reported on development of a murine model with G-CSF receptor mutations. McLemore and colleagues in St. Louis, MO,<sup>4</sup> reported on a “knock-in” mouse mutation which reproduced the mutation of GCSF-R in a SCN patient. These mice did not develop an SCN phenotype and had bone marrow and blood counts which were normal for age. *In vitro* studies of colony-forming cell assays in the presence of varying concentrations of G-CSF suggested a possible hyperproliferative response to G-CSF in the presence of this truncated GCSF-R. They concluded that these mice, who carried a targeted mutation of their GCSF-R, expressed a truncated receptor in a lineage-specific manner, but did not develop an SCN phenotype. Further studies are underway to determine whether AML/MDS is increased in these mice and whether chronic administration of G-CSF will affect the latency or incidence of AML/MDS.

A second set of investigators, Hermans et al from Rotterdam,<sup>5</sup> reported on a mouse model with a GCSF-R mutation which resulted in mice with reduced numbers of circulating neutrophils, as compared with wild type littermates, but the neutropenia was not as profound as in SCN patients. Similarly, bone marrow smears from these animals did not reveal the characteristic morphological changes seen in the patients. They propose that the truncated GCSF-R leads to an altered proliferation/maturation balance consistent with the ability of the affected myeloid progenitors to clonally expand in the marrow of SCN patients.

These two papers together certainly add support to the role of the development of a GCSF-R mutation as a potential step towards leukemogenesis in patients with SCN.

#### ***Other Publications of Interest from ASH 1997***

Further information regarding the use of G-CSF in pediatric patients with chronic idiopathic neutropenia can be found in an article by Bernini et al in the *Journal of Pediatrics*.<sup>6</sup> These investigators studied a group of six children with symptomatic chronic idiopathic neutropenia, with an aim to define the lowest possible doses of G-CSF that would benefit these children. The dose was defined by treating the children with daily G-CSF and monitoring blood work twice weekly until an ANC  $> 1.5 \times 10^9/L$  was achieved. The dose was then decreased in two alternating steps, initially doubling the interval between doses. If the ANC was maintained  $> 1.0 \times 10^9/L$ , the G-CSF dose was then reduced by 25–50%. These dose reduction steps were alternated until the lowest G-CSF dose that would maintain the ANC  $> 1.0 \times 10^9/L$  was achieved. All patients were able to be reduced to a dosage frequency ranging from once weekly to every other day. The children benefited from the medication in terms of resolution of all preexisting chronic infections, reduction in the frequency of new infectious episodes, and discontinuation of prophylactic antibiotics. The authors estimated a significant cost saving in their center by using this strategy. Although conducted on a small group of patients, the SCNIR advisory board believes that this study outlines an easy-to-follow approach to safely reducing G-CSF dosage in these patients.

### References

1. Dale DC, Cottle T, Bolyard AA, Fier C, Aitchison R, Bonilla MA, Boxer L, Catalano P, Cham B, Freedman M, Kannourakis G, Kinsey S, Mori P, Zeidler C, and Welte K for the Severe Chronic Neutropenia International Registry. Long term treatment of chronic idiopathic neutropenia with G-CSF. *Blood* 90 (10 suppl) 763.
2. Boxer L, Mori PG, Bonilla MA, Dale D, Cham B, Kinsey S, Welte K, Fier C, Catalano P, Cottle T, Kannourakis G, and Freedman M for the Severe Chronic Neutropenia International Registry. Report on patients with Shwachman-Diamond syndrome with severe chronic neutropenia. *Blood* 90 (10 suppl 1).
3. Freedman MH, Bonilla MA, Boxer L, Catalano P, Cham B, Fier C, Kannourakis G, Kinsey S, Mori PG, Shannon K, Touw I, Welte K, Dale DC for the Severe Chronic Neutropenia International Registry. MDS/AML in patients with severe chronic neutropenia (SCN) receiving G-CSF. *Blood* 88 (10 suppl 1) 1782 (abstract).
4. McLemore ML, Poutsine-Lautent J, Link DC. Mice carrying a targeted "knock-in" mutation of their G-CSF receptor that reproduces the mutation observed in a patient with severe congenital neutropenia exhibit normal basal granulopoiesis. *Blood* 90 (10 Supp 1) 1918 (abstract).
5. Hermans MHA, Antonissen C, Karis A, Ward AC, de Jongh C, Touw IP. Mice with a targeted G-CSF receptor mutation derived from severe congenital neutropenia have reduced absolute neutrophil counts but are not severely neutropenic. *Blood* 90 (10 suppl 1) 1822 (abstract).
6. Bernini JC, Wooley R, Buchanan GR. Low-dose recombinant human granulocyte colony-stimulating factor therapy in children with symptomatic chronic idiopathic neutropenia. *Journal of Pediatrics* 129:551-558, 1996.

### 1997 Annual Report Synopsis

#### Enrollment

Through December 31, 1997, there were 531 patients (congenital 249, idiopathic 176, cyclic 106) from 13 countries enrolled in the Registry; 60% were less than 18 years of age.

#### Treatment Response

Longitudinal data from the SCNIR demonstrates that, with continued Filgrastim treatment, the increased neutrophil level can be maintained for at least nine years. Statistics for median daily dose for all patients by diagnosis (maximum duration of 9 years) is shown in Table 1.

TABLE 1.

**Median Daily Filgrastim Dosing (mcg/kg/day)\***

CLASSIFICATION	MEAN (SD)	MEDIAN	RANGE
Congenital n=206	14.9 (24.7)	6.9	0.2-240.0
Cyclic n=91	2.6 (2.1)	2.2	0.1-11.2
Idiopathic n=116	2.4 (5.2)	1.2	0.1-51.4
Total n=413	8.7 (18.7)	3.4	0.1-240.0

\*Include all patients with sufficient data to calculate a daily dosage

**Thrombocytopenia**

During this reporting period, thrombocytopenia (platelet count  $< 50 \times 10^9/L$ ) among Filgrastim-treated patients was reported at a patient incidence of 3.9% (11/285); thrombocytopenia also occurred at baseline and/or at times without Filgrastim administration and was attributed to the patient's underlying disease. Data continue to support the conclusion that thrombocytopenia remains an infrequent occurrence during treatment with Filgrastim ( $< 6\%$ ); it was more often seen in patients with congenital types of neutropenia and onset was not related to increased duration of Filgrastim therapy. Most cases of thrombocytopenia were managed with a reduction or interruption of Filgrastim.

**Development of Leukemia**

The development of cytogenetic abnormalities, myelodysplasia and leukemia remain the issue of greatest concern. Results to date suggest that patients with congenital neutropenia are predisposed to leukemic transformation, but the mechanism of their susceptibility remains unknown. In the pre-cytokine era, many congenital neutropenia patients died in the first years of life from infection. With Filgrastim therapy, most patients have not developed life-threatening infections and have survived well beyond two years of age. It therefore cannot be known if this increased survival allows for a higher risk for the recognized natural expression of leukemogenesis in this population in the absence of Filgrastim therapy.

As of Dec. 31, 1997, leukemic transformations have occurred only in the congenital neutropenia patients; no leukemic transformations have occurred among patients with cyclic or idiopathic neutropenia. Among patients with congenital neutropenia, the crude rate for development of MDS/AML is 8.9%. A life table analysis revealed that the cumulative risk of developing leukemia or MDS by the end of the 8th year of Filgrastim treatment in a patient with congenital neutropenia was 16.5% (95% C.I. = 9.8-23.3%); this represents an annual rate of approximately 2%. An analysis of age at conversion showed the highest proportion of cases occurred in patients 10 to 20 years of age. No apparent trends were found between the leukemic conversion rate with age and duration of Filgrastim administration. The stepwise acquisition of monosomy 7, RAS oncogene mutations, and G-CSF receptor mutations in

some patients with congenital neutropenia indicate a genetic predisposition to malignant transformation. Annual marrow cytogenetic testing to identify monosomy 7 or other changes indicating transformation is highly recommended in patients with congenital neutropenia.

### ***Splenomegaly***

Baseline splenomegaly was reported in 23% of congenital neutropenia patients. During the initial few years of Filgrastim therapy, the prevalence of splenomegaly increases up to 48.8%, with a median palpable spleen size of 2–4 cm below the costal margin (BCM). The maximum prevalence rate among patients with cyclic and idiopathic neutropenia is not as high either at baseline (13% and 8.8%, respectively) or during eight years of Filgrastim therapy (5.9% and 11.1%, respectively). The degree of splenomegaly with increased duration of Filgrastim therapy is variable. In some individuals, splenomegaly is associated with their underlying disease and its progression, concurrent with severe infection, or in association with leukemic transformation.

### ***Osteopenia/Osteoporosis***

Osteopenia/osteoporosis was reported in 14.5% (77/531) of SCN patients (congenital 58, cyclic 6, idiopathic 13). Many of these reports (37) were based only on an abnormal bone density measurements and it is unknown how many patients have clinical symptoms. No correlation was found between Filgrastim dosing and the development of osteopenia or osteoporosis. Diagnostic procedures for bone density evaluation have not been reported in 70% of Registry patients, thus the actual incidence remains unknown. In an effort to better quantify the true incidence and severity of osteopenia/osteoporosis, the Registry is collecting additional detailed data on patients for whom osteoporosis is reported as a clinical problem, and for those with reports of abnormal bone density results.

### ***Vasculitis***

Vasculitis has been reported in 4% of SCNIR patients; it is reported at a slightly higher rate among patients with idiopathic neutropenia (5%), compared to patients with congenital and cyclic types of neutropenia (2.4% and 2.8%, respectively). In the Amgen-sponsored SCN clinical trials, a 3% incidence of cutaneous vasculitis was reported. In these patients, lesions were usually limited to the skin; over half of these cases were biopsy-proven leukocytoclastic vasculitis. Symptoms of vasculitis generally developed simultaneously with an increase in ANC and abated when the ANC decreased. Most patients were able to continue Filgrastim at the same or a reduced dose. The mechanism of vasculitis in these patients is unknown. The Registry is utilizing a questionnaire to collect additional data on the extent of involvement, course and treatment of vasculitis.

### ***Growth and Development***

Analysis of growth and development parameters show that children with SCN are shorter than persons in the normal population; 35–52% of children were at less than the 10th percentile of

normal height for age. This difference in height (shorter than normal) persists with Filgrastim treatment and is more significant among patients with congenital neutropenia, as compared to cyclic and idiopathic types of neutropenia; thus suggesting a relationship to severity of illness. Previous analyses have identified a trend for beneficial effect of earlier treatment on height, however, this trend has not yet been shown to be statistically significant.

### ***Pregnancy and Fertility***

The Registry has data on 21 pregnancies among Filgrastim-treated patients, 16 resulted in live births and five were terminated (4 due to complications). Of the 16 live births, 13 neonates were normal, and three had abnormalities. Congenital types of abnormalities were detected in a total of four of these pregnancies, one during embryogenesis and three at birth (renal 1, cardiac 1, renal and cardiac 1). Thirty-three percent (7/21) of pregnancies during which the mothers received Filgrastim treatment resulted in complications. The data from these few case reports in patients with SCN are inconclusive regarding use of Filgrastim during pregnancy, further information is still required in order to better understand the possible effects which Filgrastim may have on reproductive function and embryogenesis.

### ***Mortality***

A cumulative review of all deaths among SCN patients reported either during clinical trials or Registry observation revealed the leading diagnosis at time of death was complications secondary to leukemic conversion (n=23). The second most frequent diagnosis was infection (n=19). Median age at death was 17.3 (range 0.33 to 83.9) years. Eight of these deaths occurred during 1997, none of which were reported as related to Filgrastim.

### ***Observation of Other Adverse Events***

No trend for new or unusual adverse events was found during this reporting period.

### ***List of 1997 SCNIR Abstracts***

Boxer L, Mori PG, Bonilla MA, Dale D, Cham B, Kinsey S, Welte K, Fier C, Catalano P, Cottle T, Kannourakis G, Freedman M: Report on patients with Shwachman-Diamond syndrome with severe chronic neutropenia [abstract]. *Blood* 1997, 90 (suppl 1): 3544.

Dale DC, Cottle T, Bolyard AA, Fier C, Aitchison R, Bonilla MA, Boxer L, Catalano P, Cham B, Freedman M, Kannourakis G, Kinsey S, Mori P, Zeidler C, Welte K. Long term treatment of chronic idiopathic neutropenia with G-CSF [abstract]. *Blood* 1997, 90 (suppl 1): 763.

Davis RL, Cottle T, Bonilla MA, et al. Growth among patients with severe chronic neutropenia treated with Filgrastim (G-CSF). *Fed Clin Res Abstract*. Submitted.

Welte K, Touw IP. G-CSF receptor mutations in patients with severe chronic neutropenia: A step in leukemogenesis? [abstract]. *Blood* 1997, 90 (suppl 1): 1921.

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## Questions Frequently Asked by Treating Physicians

### 1. Why is it necessary to monitor patients with blood work three times per week for 6 weeks prior to establishing a diagnosis of cyclic neutropenia?

*Cyclic neutropenia can only be diagnosed by doing serial blood counts, plotting the characteristic oscillations and then comparing them with the symptom profile. As yet, there is no genetic test for this disease. The term "cyclic neutropenia" should be used only for patients with very regular oscillations at approximately 21-day intervals, with the counts falling to less than 200 for several days within each cycle. This definition encourages some degree of uniformity in diagnosis. When the period length appears to be shorter or longer and the nadirs not so deep, the disease is often referred to as idiopathic, rather than cyclic, neutropenia.*

*There are several reasons why it is important to make a specific diagnosis of cyclic neutropenia, if at all possible.*

*Severe chronic neutropenia is a heterogeneous disorder. Within the SCNR, SCN has been classified into three broad groups: congenital, cyclic and idiopathic. As data is collected, it is important to have these groups as accurately characterized as possible, because the natural history of the disease and potential implications for the patient will vary, depending on the diagnostic group in which they fall.*

*It has become apparent by analyzing the data to date that patients with congenital neutropenia have an increased risk of developing MDS/AML, as compared to the other diagnostic groups. By ensuring that patients are accurately diagnosed and classified, it has been possible to make the recommendation that patients with cyclic neutropenia do not need annual surveillance bone marrow examinations with cytogenetics, as they do not appear to be at risk of developing this complication.*

*The natural history of each subgroup is different. By specifically diagnosing a patient within one of the groups, your ability to counsel the patient regarding the natural history of their disorder is greatly enhanced. This disease causes recurrent fevers and severe symptoms and infections in most affected individuals. It is now known that patients with cyclic neutropenia are responsive to treatment with G-CSF and have benefited from reductions in the number and severity of infections experienced. Patients not on treatment are at risk of death from severe infections. Thus, there is direct benefit to the patients.*

*Patients need to know the diagnosis so that they may be treated appropriately. There are many other causes for neutropenia, some where G-CSF is not indicated. Knowing the specific cause allows the physician to make an accurate diagnosis and institute proper therapy.*

### 2. Are there specific groups of patients who appear more likely to develop thrombocytopenia while on G-CSF, and what is the appropriate management of this development?

*Since initiation of the SCNR, 31 of 446 patients have reported thrombocytopenia (platelet count <50,000). Twenty-seven of these patients were receiving G-CSF and four were untreated at the time of onset. Twenty-two of these patients had the diagnosis of congenital neutropenia (including Shwachman-Diamond syndrome = 2, glycogen storage disease 1b = 1 and myelokathexis = 1), five had cyclic and four had idiopathic types of neutropenia. Therefore, the group at highest risk appears to be patients with congenital neutropenia. In the past year, of the 7 patients reported to have thrombocytopenia, 5 also had splenomegaly; the mechanism of thrombocytopenia in at least some of these patients may be hypersplenism.*

*Most patients who have developed platelet counts less than 50,000 have been successfully managed by reducing or interrupting the dose of G-CSF. However, thrombocytopenia may also be an indication of developing MDS/AML or acquired cytogenetic changes, and persistent thrombocytopenia warrants further investigation.*

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