

- What's New in Severe Chronic Neutropenia
- 2002 Demographic Table
- 2002 State and Country Tables
- 2002 Deaths

## Severe Chronic Neutropenia International Registry

### Physician Newsletter

The years 2000 - 2002 have been an exciting transition period for the Severe Chronic Neutropenia International Registry. For our first six years, we were funded through research contracts with Amgen. We have now become an independent research center, based at the University of Washington, funded principally through the Amgen Foundation. This support will enable us to operate for another five years, and we expect to find other sources of funding to continue our activities.

This is a good time to reflect on the accomplishments of the Registry. These accomplishments are, of course, only possible with the continued assistance and cooperation of our patients and their physicians. The numbers of patients registered, and the timely submission of data and samples, has enabled us to learn a great deal about patients with severe chronic neutropenia. This would have been accomplished only with great difficulty by individual physicians, or even geographically based groups of physicians, working with their own patients.

In 2001, we were fortunate in recruiting four new members to join the Advisory Board of the Severe Chronic Neutropenia International Registry; Drs. Blanche Alter (NIH), Jean Donadieu (Hospital Trousseau, Paris, France), and Jerry Winkelstein (Johns Hopkins, Baltimore, MD, USA). We also welcomed Ms. Lee Reeves of Pinckney Michigan, USA, who is a parent of a daughter who suffered from severe chronic neutropenia. Ms. Reeves is a very welcome addition to our board. We extend our appreciation to Prof G. Mori who is no longer on the Advisory Board but was a valuable board member for several years.

We published a handbook of information for patients and their families. The English language version is currently being distributed via a link from the Registry website at: <http://depts.washington.edu/registry/>, and has been translated into seven other languages, thus far. A physician guide to severe chronic neutropenia is currently in development and will be published to the Registry's web site above within a year.

## What's New in Severe Chronic Neutropenia?

### Mutations in the Gene for Neutrophil Elastase

The past several years have seen a number of publications regarding severe chronic neutropenia. An important discovery from Dr. David Dale's group in Seattle was first presented at ASH in December 1999. They reported that they had mapped the locus for autosomal dominant cyclic neutropenia to chromosome 19p13.3 and identified mutations in the neutrophil elastase gene in a number of patients with cyclic neutropenia<sup>1</sup>. They subsequently expanded this work to include patients with congenital neutropenia. The report in the October 2000 issue of *Blood* indicated that 22/25 patients with congenital neutropenia who were tested had mutations of the elastase gene. Interestingly the mutations in patients with cyclic neutropenia tended to cluster near the active site of the molecule whereas the opposite face was predominantly affected by the mutations found in congenital neutropenic patients. The identification of the mutation of this gene in patients with both congenital neutropenia and cyclic neutropenia raises as many questions as it answers regarding the potential mechanisms by which neutropenia occurs in these disorders. Further research will be needed to clarify these questions.

Dr. Dale and his group have more recently published a summary of their findings and included a proposed model for the cellular abnormalities of hematopoiesis in congenital neutropenia based on the mutant neutrophil elastase.<sup>3</sup> They propose that neutrophil differentiation in cyclic and congenital neutropenia is associated with synthesis of normal and mutant neutrophil elastase. Formation of the mutant enzyme induces accelerated apoptosis of the developing cells of the neutrophil lineage. The resultant neutropenia leads to an increased feedback stimulation of hematopoietic stem cells and this high proliferative activity creates the vulnerability for the evolution to MDS/AML observed in congenital neutropenia (discussed below). This short commentary is an interesting one to read.

### Risk of Leukemia

In *Blood*<sup>4</sup>, July 2000, Dr. Mel Freedman, on behalf of the SCNIR, published a paper re-

garding the occurrence of myelodysplasia and AML in patients with congenital neutropenia receiving G-CSF. This paper summarizes data collected through the registry and pre-registry clinical trial data showing a crude rate of 9% malignant transformation in patients with congenital neutropenia receiving G-CSF. There have been no cases of MDS/AML reported in patients with glycogen storage disease type 1b (another subgroup of congenital neutropenia). There also have been no reported cases of MDS/AML in any SCNIR patients with cyclic or idiopathic neutropenia who have been treated with G-CSF for up to 11 years. This is interesting in relation to the finding that the same gene may be mutated in both congenital and cyclic neutropenia, albeit in different locations.

The SCNIR data on 352 patients with congenital neutropenia shows that severe bacterial complications have been almost completely eliminated in more than 90% of patients with G-CSF therapy, and death from sepsis is now a very unusual, if not rare, event. Thus, the natural history of congenital neutropenia has been sharply altered by G-CSF therapy. These patients have a vastly improved survival rate and are living longer. The Registry therefore recommends that G-CSF as specific therapy for all forms of severe chronic neutropenia. It should be the initial treatment for this family of disorders. However, careful surveillance and serial monitoring of clinical, hematological, and cytogenetic parameters, including yearly bone marrow examinations in congenital neutropenic patients, are urged.

Another article, published in 2001 by Banerjee and Shannon<sup>5</sup>, looks at leukemic transformation in this group of patients. These authors raise the question as to whether ELA2 might act as tumor suppressor gene in leukemogenesis.

### Pregnancy in SCN Patients

Dr. Larry Boxer first summarized the experience of G-CSF administration during pregnancy in patients with severe chronic neutropenia in an abstract published in 1999<sup>6</sup>. Review of SCNIR records revealed 115 pregnancies in 48 SCN mothers. Seventeen of these

Dr. Dale's group in Seattle...mapped the locus for autosomal dominant cyclic neutropenia to chromosome 19p13.3..."

patients received G-CSF for a median of 2 trimesters. Outcomes included 12 live births, 3 elective terminations, and two spontaneous abortions. All 12 neonates were healthy without physical abnormalities or major medical complications although five had neutropenia. In addition to the SCNIR cases, Amgen's clinical safety department has received 12 post-market (retrospective) reports of pregnancy among non-Registry SCN patients, 9 with G-CSF exposure and 3 without. Outcomes among the 0 treated pregnancies included 7 live births and two terminations (one spontaneous abortion at 5 weeks of gestation and one induced termination subsequent to abnormal embryogenesis revealed on an ultrasound at 8 weeks gestation). The 7 live births included 4 normal neonates without major medical complications and 3 neonates with renal/ and / or cardiac abnormalities. The recommendation from the Registry is still that G-CSF therapy during pregnancy should be reserved for mothers who are significantly affected by their neutropenia, and should be withheld during the first trimester if at all possible.

#### Treatment Recommendations

Another abstract published in the ASH abstract book in 1999<sup>7</sup>, authored by Dr. Sally Kinsey on behalf of the SCNIR outlined the recommendations for therapy which have been developed by the Advisory Board. The recommendations are as follows:

G-CSF should be considered to be the first line therapy for patients with symptomatic severe chronic neutropenia. We recommend commencing G-CSF at a dose of 3 – 5 mcg/kg/day. The patients should be monitored during the first 14 days and the dose titrated to maintain an absolute neutrophil count (ANC) of 1.0- 5 x 10<sup>9</sup>/L. The dose can be increased gradually to 100mcg/kg/day if a response is not seen. Each dosage level should be maintained for at least 14 days with several determinations of the ANC during that period in order to assess response. If no response is achieved then consideration should be given to hematopoietic stem cell transplantation (HSCT) from an HLA identical sibling or other suitable donor. Combination therapy with G-CSF ± prednisone has not yet proven to be effective for long-term therapy. Patients who develop monosomy 7, other chromosomal abnormalities or MDS/AML should proceed to urgent HCST.

“G-CSF should be considered to be the first line therapy for patients with symptomatic severe chronic neutropenia.”

What is the experience with HSCT in patients with severe chronic neutropenia? We know from past experience that once myelodysplastic syndrome or leukemia has developed the outcome following this therapy is very poor (77% mortality in the SCNIR) (data from the SCNIR annual report, 1997). Because of these data, Dr. Connie Zeidler, in collaboration with Dr. John Levine, reviewed the experience of HSCT in patients with SCN without evidence of leukemic transformation in a publication in *Blood*, February 2000<sup>8</sup>. They reported on a total of 11 patients with congenital neutropenia, who had been reported to the SCNIR, and who had undergone transplantation for reasons other than malignant transformation between 1976 and 1998. Eight of these patients had HSCT from an HLA matched sibling donor and are alive as of publication of the article. Three patients were transplanted using alternative donors. These transplants were considerably more complicated and only 1/3 patients have survived. It is based on this experience that the recommendations for HSCT in refractory patients outlined above have been developed. Further work is underway to develop a uniform approach to alternative donor selection, conditioning regimes, and supportive care for these patients.

#### Glycogen Storage Disease

Three groups have reported on the response to therapy of patients with glycogen storage disease 1b (GSD 1b) and neutropenia in the last two years. Dr. Stan Calderwood summarized the experience of 13 patients treated with G-CSF over a duration of 3 years in a publication in *Blood*, January 2001<sup>9</sup>. They found a significant increase in circulating neutrophil numbers and an improvement in neutrophil function as assessed in vitro following therapy. They had no cases of myelodysplasia or marrow exhaustion. They reported that therapy was associated with objective and subjective improvement in infection-related morbidity. All patients developed splenomegaly as assessed by clinical examination, and five of the patients developed hypersplenism (defined in this study as thrombocytopenia (platelet count less than 150 x 10<sup>9</sup>/L) present on at least 2 consecutive complete blood counts at least one month apart, in association with splenomegaly). Thrombocytopenia was mild. One patient underwent splenectomy for presumed hemolytic anemia that was subsequently diagnosed to be due to

vitamin B12 deficiency. These authors concluded that their data supported the short-term safety and efficacy of G-CSF therapy for GSD type 1b patients and that monitoring of the splenomegaly is needed on a continuing basis.

The safety and efficacy of G-CSF for this group of patients was also confirmed by Dr. George Kannourakis in a poster at ASH in December 2000<sup>10</sup> based on 33 patients with GSD 1b and neutropenia enrolled in the SCNIR. These patients have been treated for a median duration of 65 months (range 8-114 months) with a median dose of 3.1 mcg/kg/day. All patients responded with an increase in ANC. Palpable splenomegaly developed in 100% of patients by four years of therapy. The splenomegaly often responds to a decreased in G-CSF dose. Hypersplenism was reported in six patients, of whom 3 underwent splenectomy. Three patients died during this period of infection. Of these two had had splenectomy. The authors concluded that long-term administration of G-CSF is a safe therapy for this group of patients but that splenectomy should be approached with caution due to the possibility of post-splenectomy sepsis.

Finally, a recent report from the European Study on Glycogen Storage Disease Type I<sup>11</sup> reported on 18 patients who received G-CSF for up to 7 years, as well as 39 untreated patients. They note that in all patients treated, the number and severity of infections decreased. They also commented on splenomegaly. They found a beneficial effect on the inflammatory bowel disease often seen in these patients.

#### Idiopathic Neutropenia

The Registry presented a summary of data regarding long treatment of chronic idiopathic neutropenia in women with G-CSF at ASH in 2001.<sup>12</sup> Of the 832 patients enrolled on the registry, 288 are diagnosed with idiopathic neutropenia and 68.4% of these are women. For the patients for whom data is available, the median dose of rhuG-CSF is 1.5 mcg/kg/day and the patients had been treated for a median duration of 6.7 years. Some of these patients have developed arthritis, proteinuria/hematuria, and vasculitis and this may be due to any underlying autoimmune disorder. There have been no reports of myelodysplastic syndrome or leukemia in these patients.

Bolyard et al conclude from their review of the data that rhuG-CSF is a very effective long term therapy for female patients with chronic idiopathic neutropenia and most patients require only small doses to increase the absolute neutrophil count to normal range and to avoid recurrent febrile illnesses.

#### Glomerulonephritis in Patients with Severe Chronic Neutropenia

Boxer et al reported at ASH in 2000 about the development of glomerulonephritis in patients with SCN 13. The authors noted that there is a baseline of approximately 5% incidence of renal abnormalities in patients with SCN who are not treated with rhuG-CSF but that this does increase slightly with therapy. In reviewing the registry, twenty five patients with glomerulonephritis, proteinuria or persistent hematuria over 12 months were reported in a five year period. Of these, 12 cases were attributed to underlying process such as urinary tract infection, autoimmune and congenital disorders, diabetes, and post bone marrow transplant complications. Symptoms resolved in 3 out of 5 patients for whom the rhuG-CSF dose was decreased. Thirteen patients had no obvious underlying etiology for the renal abnormalities and seven of these had renal biopsies performed. Of these, immune deposits were demonstrated in 6 samples, and a possible diagnosis of systemic lupus was made in the 7<sup>th</sup>. They concluded that the patient incidence of renal abnormalities appears to increase with rhuG-CSF treatment duration in patients with congenital but not cyclic or idiopathic neutropenia. In congenital patients with these symptoms, renal biopsy with evaluation for immune complex deposits is indicated. Although the role of rhuG-CSF is undefined within these syndromes, some of the patients benefited from a reduction in dose or temporary withdrawal of the medication, and a trial of dose alteration should be considered in such patients.

#### A New Summary of SCN

Finally, we bring to your attention a recent volume of Seminars in Hematology (April 2002, Vol 39, no 2) summarizing all our knowledge about severe chronic neutropenia. These are ten articles written by authors associated with the Registry. The articles cover a range of topics including the mechanisms, diagnosis and treatment of severe chronic neutropenia.

### References

1. Horwitz M, Benson K, Person R, Aprikyan A, Dale D. The molecular basis of cyclic hematopoiesis. *Blood*, 1999;94:abs 2885.
2. Dale DC, Person RD, Bolyard AA, Aprikyan AG, Bos C, Bonilla MA, Boxer LA, Kannourakis G, Zeidler C, Welte K, Benson KF, Horwitz M. Mutations in the gene encoding neutrophil elastase in congenital and cyclic neutropenia. *Blood*, 2000;96:2317-2322.
3. Dale DC, Liles WC, Garwicz D, Aprikyan A. Clinical implications of neutrophil elastase in congenital and cyclic neutropenia. *Journal of Ped Hem/Onc*, 2001;23:208-210.
4. Freedman MH, Bonilla MA, Fier C, Bolyard AA, Scarlata D, Boxer LA, Brown S, Cham B, Kannourakis G, Kinsey SE, Mori PG, Cottle T, Welte K, Dale DC. Myelodysplasia syndrome and acute myeloid leukemia in patients with congenital neutropenia receiving G-CSF therapy. *Blood*, 2000;96:429-436.
5. Banerjee A, Shannon K. Leukemic transformation in patients with severe congenital neutropenia. *Journal of Ped Hem/Onc*, 2001;23:487-495.
6. Boxer LA, Dale DC, Bonilla MA, Bolyard AA, Chan Bonnie, Freedman M, Kannourakis G, Schwinzer B, Fier C, Brown S, Welte K. Administration of r-metHuG-CSF during pregnancy in patients with severe chronic neutropenia (SCN). *Blood*, 1999; 94:abs 3948.
7. Kinsey SE, Bolyard AA, Bonilla MA, Boxer L, Brown S, Dale DC, Cham B, Fier C, Freedman G, Kannourakis G, Mori P, Welte K, Zeidler C. Algorithm for the management of Kostmann's neutropenia based on data from the severe chronic neutropenia international registry. *Blood*, 1999;94:abs 3955.
8. Zeidler C, Welte K, Barak Y, Barriga F, Bolyard AA, Boxer L, Cornu G, Cowan MJ, Dale DC, Flood T, Freedman M, Gardner H, Mandel H, O'Reilly RJ, Ramenghi U, Reiter A, Skinner R, Vermeylen C, Levine JE. Stem cell transplantation in patients with severe congenital neutropenia without evidence of leukemic transformation. *Blood*, 2000;95:1195-1198.
9. Calderwood S, Kilpatrick L, Douglas SD, Freedman MH, Smith-Whitley K, Rolland M, Kurtzberg J. Recombinant human granulocyte colony-stimulating factor therapy for patients with neutropenia and/or neutrophil dysfunction secondary to glycogen storage disease type 1b. *Blood*, 2001;97:376-382.
10. Kannourakis G, Cottle T, Bolyard AA, Bonilla MA, Boxer LA, Cham B, Dale DC, Fier C, Kinsey SE, Liang B, Mori PG, Welte K. Long term follow-up on patients with glycogen storage disease 1b and severe chronic neutropenia treated with G-CSF. *Blood*, 2000;96:abs. 1267.
11. Visser G, Rake JP, Labrune P, Leonard JV, Moses S, Ulrich K, Wendel U, Groenier KH, Smit GP. Granulocyte colony-stimulating factor in glycogen storage disease type 1b. Results of the European Study on Glycogen Storage Disease Type 1. *Eur J Pediatr*, 2002;161:S83-7.
12. Audrey Anna Bolyard, Tammy Cottle, Mary Ann Bonilla, Lawrence A. Boxer, Bonnie Cham, Jean Donadieu, Carol Fier, Melvin H. Freedman, George Kannourakis, Sally Kinsey, Bertrand Liang, Beate Schwinzer, Cornelia Zeidler, Karl Welte, David C. Dale. Long Term Treatment of Chronic Idiopathic Neutropenia in Women with G-CSF. *Blood*, 2001; 98: abs 1265.
13. L. Boxer, C. Fier, A. Bolyard, M. Bonilla, S. Brown, B. Cham, M. Freedman, G. Kannourakis, S. Kinsey, P. Mori, C. Zeidler, K. Welte, D.C. Dale. Development of Glomerulonephritis in patients (pts) with severe chronic neutropenia (SCN). *Blood* 2000: 96: abs 1284.

**Do Not Put On Website Yet**  
**Patient Demographics**  
**By Diagnosis**  
**2002**

	Congenital n=481 n(%)	Cyclic n=194 n(%)	Idiopathic n=366 n(%)	Total n=1041 n(%)
<b>Age (years)</b>				
Mean	15.6	25.6	32.7	23.5
Standard Deviation	10.4	17.8	23.7	19.1
Median	13.7	20.2	28.6	17.3
Range	1.8-74.0	1.9-79.9	1.8-93.4	1.8-93.4
<b>Age Category</b>				
Pediatric (< 18 years)	328 (68.2)	82 (42.3)	129 (35.2)	539 (51.8)
Adult (>= 18 years)	153 (31.8)	112 (57.7)	237 (64.8)	502 (48.2)
<b>Sex</b>				
Male	260 (54.2)	86 (44.3)	123 (33.6)	469 (45.1)
Female	221 (45.9)	108 (55.7)	243 (66.4)	572 (54.9)
<b>Race</b>				
Caucasian	387 (80.5)	171 (88.1)	324 (88.5)	882 (84.7)
Black	22 (4.6)	5 (2.6)	5 (1.4)	32 (3.1)
Asian	17 (3.5)	2 (1.0)	5 (1.4)	24 (2.3)
Hispanic	26 (5.4)	6 (3.1)	8 (2.2)	40 (3.8)
Unknown	29 (6.0)	10 (5.2)	24 (6.6)	63 (6.1)

Patient Demographics  
By State  
2002

State	Total Enrolled	Population* Prevalence	State	Total Enrolled	Population* Prevalence	State	Total Enrolled	Population* Prevalence
AK	2	3.19	KY	4	0.99	NY	32	1.69
AL	6	1.35	LA	1	0.22	OH	25	2.20
AR	3	1.12	MA	15	2.36	OK	4	1.16
AZ	6	1.17	MD	8	1.51	OR	9	2.63
CA	70	2.07	ME	0	0.00	PA	26	2.12
CO	11	2.56	MI	46	4.63	RI	1	0.95
CT	9	2.64	MN	22	4.47	SC	9	2.24
DC	0	0.00	MO	9	1.61	SD	1	1.32
DE	0	0.00	MS	6	2.11	TN	7	1.23
FL	21	1.31	MT	6	6.65	TX	33	1.58
GA	13	1.59	NC	18	2.24	UT	11	4.93
HI	4	3.30	ND	3	4.67	VA	9	1.27
IA	5	1.71	NE	2	1.17	VT	1	1.64
ID	12	9.27	NH	1	0.81	WA	43	7.30
IL	24	1.93	NJ	16	1.90	WI	7	1.31
IN	21	3.45	NM	1	0.55	WV	3	1.66
KS	2	0.74	NV	10	5.00	WY	0	0.00

\*Number of registered SCN cases per million population based on 2000 US census.

Patients By Country 2002			
Country	Enrolled	Country	Enrolled
Australia	64	Honduras	1
Canada	43	New Zealand	1
Chile	9	Puerto Rico	3
Costa Rica	1	US	598
Cuba	1		
		Total Enrolled	721
		Clinical Trial Patients*	63
		Total Seattle DCC	784
*Non-enrolled patients from prior Amgen Studies.			

Severe Chronic Neutropenia International Registry  
 Plaza 600 Building  
 600 Stewart Street  
 Suite 1503  
 Seattle, WA 98105  
 Phone: (206) 543-9749  
 Toll Free: (800) 726-4463  
 Fax: (206) 543-3668  
 Email: [registry@u.washington.edu](mailto:registry@u.washington.edu)